HEALTH OUTCOMES ASSOCIATED WITH COGNITIVE IMPAIRMENT

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To my family.

Who know me better than I know myself.

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ABSTRACT

In this thesis, we aimed to determine whether persons with cognitive impairment no dementia (CIND) were at higher risk for negative health outcomes, and if so, to stratify persons with CIND into high and low risk groups. We also aimed to determine the whether persons with CIND had a higher risk of negative health outcomes based on their underlying familial risk, or whether difficulties with medication played a part in the development of negative health outcomes. Lastly, we aimed to determine whether cardiovascular and antidepressant medication use modified the relationship between CIND and dementia.

In Studies I and II, non-demented stroke patients who were recruited as part of the ESPRIT trial were followed up for up to five years. In Study I, a novel method of stratifying CIND based on the severity of impairment, was compared to established MCI subtypes in the ability to predict dementia. Having CIND-moderate increased the risk of dementia more than six times (HR 6.43, CI 1.30-31.7) while having multiple domain mild cognitive impairment with amnestic components increased the risk of dementia more than five times (HR 5.77, CI 1.19-28.0).

In Study II, the effect of CIND and CIND severity on dependency, vascular events, and death were analyzed. Patients with CIND were three times more likely to become dependent (HR 3.77 CI 1.52 -9.37) and three times more prone to mortality (HR 3.27 CI 1.06-10.1). CIND severity was able to discriminate those at high risk of death, with patients with CIND-moderate (HR 3.81 CI 1.14-12.8) almost four times more likely to die as compared to non-cognitively impaired patients.

In Studies III and IV, non-demented community dwelling twins who were assessed cognitively as part of a dementia study, HARMONY, were followed up negative outcomes with population-based registers. In Study III, we investigated the effect of CIND and Subjective Cognitive Impairment (SCI) on negative outcomes. CIND predicted hospitalization for dementia, death, and hospitalization in GEE analyses but not in within-pair analyses. SCI predicted dementia in both GEE and with pair analyses but only predicted hospitalization in GEE analyses. These results suggested that the relationship between CIND and negative health outcomes is confounded by genetic and shared environmental influences while SCI is independently associated with negative health outcomes. Additionally, we found that difficulty with medication was an independent risk factor for both dementia and death.

In Study IV, we aimed to determine whether medication use was associated with dementia, and whether individuals with CIND, SCI, or depression received more medication than their unimpaired counterparts. Antidepressant use, particularly the use of Selective Serotonin Reuptake Inhibitors (SSRIs) doubled the risk of dementia regardless of depression or cognitive status. Cardiovascular medications, particularly antihypertensive and lipid lowering agents halved the risk of dementia. In addition, we find that persons with CIND and SCI received less cardiovascular and more antidepressant medications than their non-impaired counterparts.

Overall, this thesis shows that persons with CIND are at increased risk of negative health outcomes such as dementia, death, hospitalization, and disability. CIND appears to be associated with negative health outcomes both due to difficulties with medication and due to the fact that CIND acts as a marker of underlying disease processes. In addition, we find that persons with CIND get less cardiovascular medications and more antidepressant medications, both of which increase the risk of dementia. These findings suggest that persons with CIND are a high-risk group in which greater vigilance by health professionals may bring benefits.

LIST OF PUBLICATIONS

This thesis is based on the following original articles, which will be referred to in the text by their Roman numerals

I. **Narasimhalu K,** Ang S, De Silva DA, Wong MC, Chang HM, Chia KS, Auchus AP, Chen C.
Severity of CIND and MCI predict incidence of dementia in an ischemic stroke cohort
Neurology 2009: 73(22): 1866–1872

II. **Narasimhalu K,** Ang S, De Silva DA, Wong MC, Chang HM, Chia KS, Auchus AP, Chen C.
The prognostic effects of post stroke CIND and domain specific cognitive impairments in non-disabled ischemic stroke patients
Stroke 2011: 42:883-888

III. **Narasimhalu K,** Carraciolo B, Feldman AL, Bennet AM, Fratiglioni L, Gatz M, Pedersen NL
Why is Cognitive Impairment associated with negative health outcomes? (*Manuscript)*

IV. **Narasimhalu K,** Mattsson I, Johnell K, Ploner A, Carraciolo B, Fratiglioni L, Gatz M, Pedersen NL
Selective Serotonin Reuptake Inhibitors (SSRIs) may increase the risk of dementia (*Manuscript)*

CONTENTS

LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
Aß	Amyloid Beta
ATC	Anatomical Therapeutical Chemical
BDRS	Blessed Dementia Rating Scale
CIND	Cognitive Impairment No Dementia
CI	Cognitive Impairment
CDR	Cause of Death Register
CVD	Cardiovascular
DEP	Depression
DSM	Diagnostic and Statistical Manual of Mental Disorders
ESPRIT	European Australasian Stroke Prevention in Reversible Ischemia Trial
GEE	General Estimating Equations
HR	Hazards Ratio
ICD	International Classification of Diseases
MCI	Mild Cognitive Impairment
MRS	Modified Rankin Scale
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association
NINDS-AIREN	National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche en l'Enseignement en Neurosciences
NPR	National Patient Register
OCI	Objective Cognitive Impairment
OR	Odds Ratio
ORD	Ordinal Scale
PDR	Prescription Drug Register
PSCI	Post Stroke Cognitive Impairment
SCI	Subjective Cognitive Impairment
SSRI	Selective Serotonin Reuptake Inhibitors
STR	Swedish Twin Registry
TCA	Tricyclic Antidepressants
TELE	Telephone Screen for Cognitive Impairment
VAD	Vascular Dementia
VCI	Vascular Cognitive Impairment
VE	Vascular Events
USD	United States Dollars
95 % CI	Ninety five percent Confidence Interval

1 INTRODUCTION

Dementia is a progressive debilitating syndrome that can affect memory and other parts of cognitive functioning. Alzheimer's disease (AD) is the most common form of dementia, accounting for 60-70% of patients with dementia, while vascular dementia (VAD) is the second most common form of dementia.[1,2] In AD, there may be a prodromal phase in which episodic memory is affected. In recognition of this, the concept mild cognitive impairment (MCI)[3] was originally developed to describe the amnestic impairments that are commonly seen in pre-AD patients.

While it has long been recognized that the cognitive sequelae of strokes result in pre-dementia states, no specific neuropsychological patterns of cognitive impairment have been identified. Therefore, amnestic MCI does not adequately characterize the cognitive profile of cognitively impaired but non-demented stroke patients. In order to better characterize these patients and patients in the prodromal stages of other forms of non-AD dementia, a more general concept of Cognitive Impairment No Dementia (CIND) was developed[4].

In community dwelling individuals, it has been shown that persons with CIND are more likely to develop negative health outcomes such dementia, institutionalization or death[5]. The same study also found that there are twice as many people with CIND than there are people with dementia. This is an alarming statistic as it indicates that many people are at high risk of conversion to dementia in the immediate future. Within the last 4 years, estimates of the total worldwide costs of dementia have risen from 315 billion USD[6] to 422 billion USD[7]. With an increasing aging population (Figure 1 a and b), the prevalence of CIND and MCI is expected to increase. This in turn will probably result in an exponential increase in the number of dementia patients, and by extension, an exponential increase in the societal costs associated with dementia.

Therefore, it is important now more than ever, to accurately identify persons who are at high risk of developing dementia, as these are the persons who are most likely to benefit from early interventions. In addition, it is important to elucidate the possible

mechanisms and modifiable risk factors behind the progression of MCI and CIND to dementia. Knowledge of these mechanisms will enable the development of interventions that may be able to delay or prevent the onset of dementia. In addition to the large impact this may have on individuals predisposed to dementia, the development of these interventions may be able to decelerate the exponential growth of the societal costs associated with cognitive impairment.

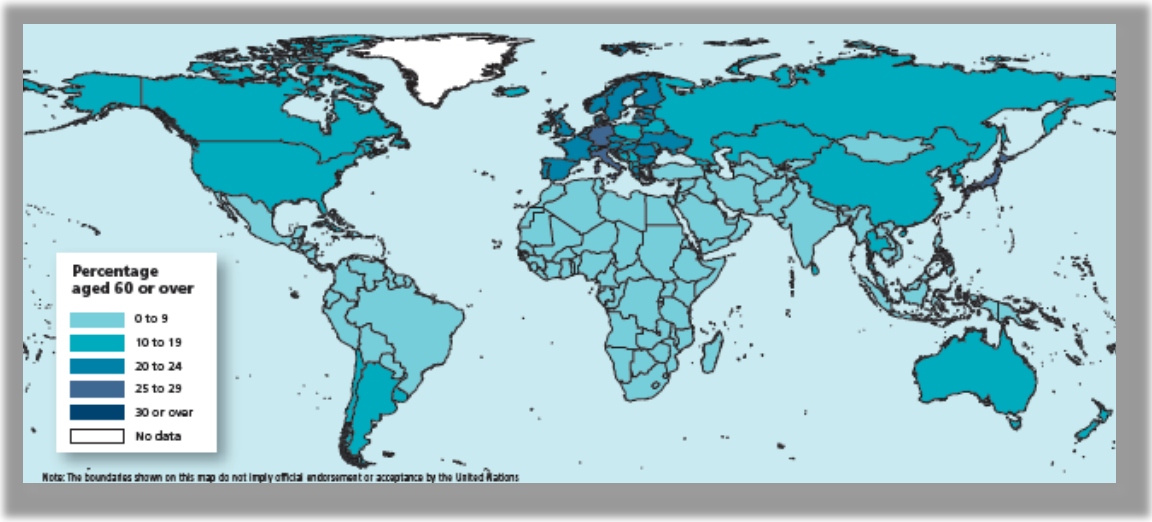

Figure 1a: Percentage of the population aged 60 and older in 2009.

Source: United Nations Population Aging and Development Chart 2009. Department of Economic and Social Affairs, Population Division, United Nations

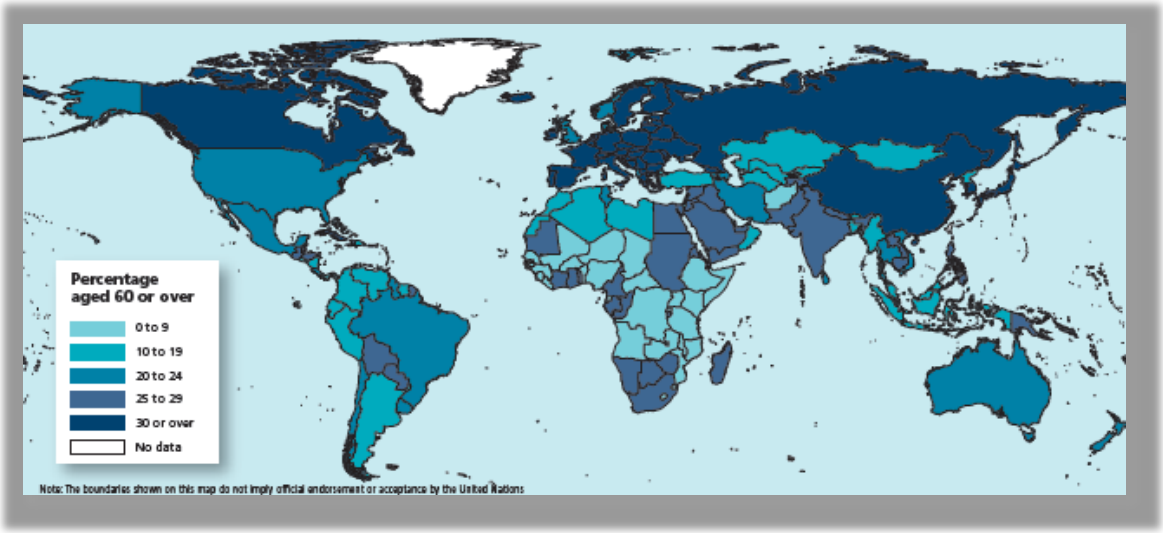

Figure 1b: Projected percentage of the population aged 60 and older in 2050.

Source: United Nations Population Aging and Development Chart 2009. Department of Economic and Social Affairs, Population Division, United Nations.

2 BACKGROUND

THE IMPACT OF DEMENTIA

Dementia is a syndrome characterized by the development of multiple progressive cognitive deficits that are severe enough to interfere with daily functioning. Epidemiological studies of dementia have shown that regardless of geographical location, both the incidence and the prevalence of dementia increase with increasing age[8]. The 2009 World Alzheimer's Report estimated that were would be 35.6 million people worldwide living with dementia in 2010, and that this number was set to double every 20 years to 65.7 million in 2030 and 115.4 million in 2050[9].

In addition to the increase in the prevalence of dementia, the societal impact is increasing. In the span of 6 years, estimates of worldwide dementia prevalence have increased by 7 million,[6,7,10] with a corresponding increase in 172 billion USD in total costs (Table 1). Even if inflation was not taken into account, the total increase in societal costs of dementia attributable to the increased prevalence between 2005 and 2009 is 57 billion USD[7].

	2003[6]	**2005[10]**	**2009[7]**
Worldwide prevalence	27.7 million	29.3 million	34.4 million
Direct costs (USD)	156 billion	210 billion	279 billion
Indirect costs (USD)	94 billion	115 billion	142 billion
Total cost (USD)	250 billion[11]	315 billion	422 billion

Table 1: Trends in worldwide costs of dementia, USD = United States Dollar

Given the large societal and individual impact of dementia, delaying or preventing the onset of dementia would have profound implications. Previous studies have suggested that if the onset of dementia is postponed for 5 years, the prevalence of dementia could be halved[12]. Therefore interventional studies are required in the pre-dementia stage so as to delay or prevent the onset of dementia. In order to more efficiently determine the efficacy of any such intervention, subgroups of persons at high risk of dementia need to be better identified.

COMMON TYPES OF DEMENTIA

Alzheimer's disease

In AD, the most common form of dementia, there is a progressive loss of neurons in several parts of the brain. Initially, this loss is limited to the hippocampal region, an area of the brain associated with memory formation[13]. Therefore, the most common initial symptom is difficulty in forming new memories, or short-term memory loss. As the disease progresses, the neuronal loss spreads first to the neocortical regions of the brain (which control higher functions such as language and spatial abilities), and then to the remaining parts of the brain. Correspondingly, patients with AD lose their language skills and their general awareness and become increasingly withdrawn.

There are two main pathological changes that have been found to associated with the development and progression of AD: amyloid-β (Aβ)-containing plaques and neurofibrillary tangles composed of hyper-phosphorylated tau[13]. In normal conditions, Aβ peptides are formed during the metabolism of amyloid precursor protein and are rapidly removed from the brain. However, when Aβ peptides are in oversupply, they aggregate to form oligomers, and are eventually deposited as plaques[14]. It has been hypothesized that the aggregated Aβ are able to damage the neuronal synapses, thereby inducing neuronal death[15]. However, the exact mechanisms behind the contribution of plaques and tangles to neuronal death are yet unknown.

In normal conditions, the tau protein is a microtubule-associated protein that is involved in stabilizing microtubules in neurons[16]. Abnormal phosphorylation of the tau protein near the C terminus of the protein results in the formation abnormal tau aggregates that in turn cause microtubule instability, and eventually, neuronal cell death. The ghosts of these aggregated hyperphosphorylated tau proteins form the neurofibillary tangles, which have been shown to be correlated with cognitive deterioration[16].

The pathological changes associated with AD are more common in persons with early onset AD than in persons with late onset AD[17]. While there is some evidence of

increased amounts of plaques and tangles in persons with late onset AD, the increase is not as marked as in persons with early onset AD. Similarly, persons with early onset AD are more likely to have a genetic basis of AD than those with late onset AD. Therefore, in most studies, early onset AD is considered a distinct entity from late onset AD. In the studies included in this thesis, the AD patients are those with late onset AD (Studies III and IV).

Vascular Cognitive Impairment

Vascular Cognitive Impairment (VCI)[18,19] encompasses a wide spectrum of cognitive impairment (mild to severe) that is presumably due to cerebrovascular disease. The etiology of the dysfunction-causing vascular lesion is diverse, ranging from symptomatic strokes, to silent infarcts, to white matter lesions, to small vessel disease. Initially, the term multi-infarct dementia was used to describe dementia that was associated with cerebrovascular disease. As the term implies, it was assumed that several infarcts contributed to the emergence of cognitive dysfunction. However, as it became apparent that single strategically placed infarcts could result in dementia in addition to large territorial infarcts, the term multi-infarct dementia evolved into VAD.

However, since there was no terminology to describe two new emerging trends: (1) the recognition of persons with CIND due to vascular causes, and (2) persons with mixed Alzheimer's and Vascular pathology, O'Brien and colleagues[18] coined the term VCI. Post stroke cognitive impairment (PSCI) is a particular form of VCI that is used to describe impairments in stroke patients that are apparent only after the stroke.

Recently, there seems to be an increasing consensus that both neurodegenerative and vascular pathologies are responsible in giving rise to dementia in the elderly. Apart from persons with early onset AD, most persons with a diagnosis of AD have some neuropathological changes that are vascular in nature[20].

STROKE

Stroke is a leading cause of mortality and morbidity worldwide.[21,22] Strokes are caused by a lack of blood to regions of the brain. The lack of blood supply can be due to a hemorrhage (hemorrhagic stroke) or a blood vessel occlusion from a clot or due to the

narrowing of the blood vessels due to atherosclerosis (ischemic stroke). As strokes often cause cell death in the regions of the brain that lack blood supply. This cell death, particularly when involving neurons, often results in physical manifestations of stroke such as weakness and numbness. These physical manifestations of stroke are often dependent on the location and severity (size of the affected region) of the stroke. While strokes commonly present with slurred speech, weakness or numbness of the face and limbs, they can also be "silent" (with no symptoms). Such silent strokes are identifiable on neuroimaging such as Magnetic Resonance Imaging (MRI) or Computer Tomography (CT) scans.

In addition to the physical symptoms of a stroke, there can be cognitive symptoms including aphasia (the inability to speak). Approximately one third of stroke patients have dementia a year after their stroke[23] and approximately a quarter have CIND[24]. Stroke patients are also twice as likely to develop dementia compared to persons without stroke[25]. Therefore stroke patients represent a high-risk subgroup of the general population for the development of dementia.

PRE DEMENTIA

Cognitive impairment can either be a person's subjective complaint of poorer cognitive functioning or an objective deficit in neuropsychological testing. A person's cognitive status can range from no cognitive impairment (NCI), to a transitional phase with some cognitive impairment, to dementia. The transitional period between NCI and dementia is commonly described using two concepts of objective deficits: MCI and CIND.

Subjective Cognitive Impairment (SCI)

Subjective Cognitive Impairment (SCI) is one measure of cognitive impairment. The effect of SCI on dementia is not firmly established, as several studies have found no association between SCI and dementia while others have found an association.[26,27] Studies that have looked at the temporal relationship between dementia shown that subjective complaints of memory impairment often precede the development of any objective cognitive deficits[26], especially in persons who are highly educated. As most of the studies that have found no association between SCI and dementia have had

shorter follow up times than the studies that found significant associations, there seems to be an increasing consensus that SCI is an early risk factor for developing dementia.

There are several challenges associated with the measurement of SCI. Firstly, there are no standardized definitions of SCI. Most current studies ask participants if they have noticed a change in their memory or cognitive well being in the preceding years (range 1-5 years). Secondly, there is no consensus as to whether the subjective complaint should be elicited from the affected individual, or from an informant. Studies have shown that there is poor correlation between the self-reported and informant-reported measures of SCI[28]. The development of a standardized tool to measure SCI would improve the ability of studies to accurately measure the predictive abilities of SCI.

Mild Cognitive Impairment (MCI)

MCI was originally identified as a precursor to AD and defined as a complaint of defective memory with an abnormal memory function for age, along with normal activities of daily living, normal general cognitive functioning and absence of dementia[3]. However, recently, a more detailed classification of MCI has been described consisting of the following four categories: amnestic MCI, non-amnestic single domain MCI, multiple domain amnestic MCI, and multiple domain non amnestic MCI[29]. These different MCI categories vary by the number of domains impaired as well as by the presence of memory impairments as detailed in the Table 2.

	Single Domain	**Multiple Domain**
Memory Impaired	Amnestic MCI	Multiple domain amnestic MCI
No memory impairment	Non amnestic single domain MCI	Multiple domain non-amnestic MCI

Table 2: MCI categories

While persons with MCI are in general at high risk of conversion to dementia, persons with amnestic forms of MCI seem to be at an even higher risk of conversion to dementia[30]. In persons with MCI, the decline in cognitive functioning seems to be paralleled by increase in disability[31]. In addition to the effect of MCI on dementia and disability, MCI seems to confer an increased risk of mortality[32]. This risk of mortality

seems to be particularly increased in persons with multiple domain amnestic MCI. However, the mechanism behind which MCI confers an increased risk of dementia, disability, and death is yet unknown.

Cognitive Impairment No Dementia (CIND)

CIND[4] is a more recent concept with a broader scope, which is used to define impairments in any objective cognitive domains in neuropsychological testing in the absence of dementia. Unlike MCI, persons with CIND do not have to have a subjective complaint in addition to an objective impairment on neuropsychological testing. Previous studies have shown that CIND may be an unstable group, with some persons with CIND progressing rapidly to dementia while others experience a more indolent course.[33,34] While previous studies have defined subtypes of CIND based on the causative etiologies,[5,35] no studies have classified persons with CIND based on severity or risk of conversion to dementia. While population based studies have shown that persons with CIND are at increased risk of dementia, hospitalization, and mortality[5], the mechanisms behind this increased risk are unknown.

Controversies and developments in pre-dementia nomenclature

There has been much debate as to the standardization of the various current definitions of pre-dementia[36]. Within a specific concept, for example, MCI, there can be variation in several aspects such as the tests and cutoffs used to derive MCI status, the etiology behind the MCI, and the effect of age, education, and cultural standards on the measurement of MCI. Additionally, even if the same tests are used in different studies, the same test may be considered a test of executive function in one study while it may be considered a test of visual abilities in another study. These inconsistencies make it difficult to compare results across studies. However, standardization is also not entirely possible due to the effect of culture, language, and education in the measurement of cognitive functioning.

Recently, the National Institute of Aging and the Alzheimer's association have published updated recommendations regarding diagnostic criteria for AD and MCI due to AD[37]. The new criteria incorporate clinical, pathological, radiological and biomarker

information in order to better characterize the level of impairment in persons with AD and MCI due to AD. The characterization of biomarkers in persons with pre-dementia may provide a basis by which studies that use differing neuropsychological tests may be compared.

For the purposes of this thesis, persons with either MCI or CIND or will be referred to as persons with objective cognitive Impairment (OCI) while persons with subjective complaints of memory disturbances will be referred to as having SCI. In addition, persons with either SCI or OCI will be referred to as having cognitive impairment (CI).

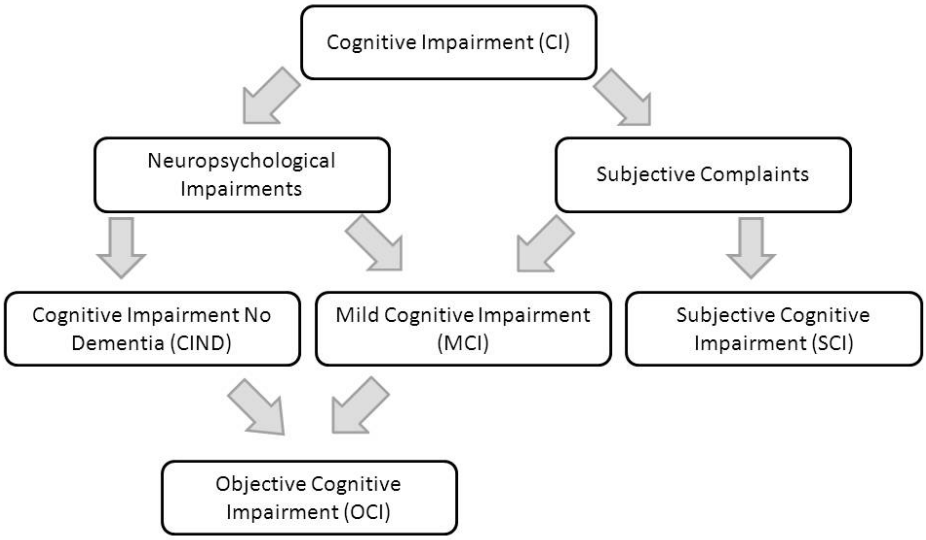

Figure 2: Cognitive Impairment definitions used in this thesis

DEPRESSION AND DEMENTIA

Several studies have shown that persons with late life depression have an increased risk of dementia. However, there has been an ongoing debate as to whether depression is a prodrome or a risk factor for dementia[38]. Recent studies suggest that late-life depression may be a prodrome rather than a risk factor for dementia[39]. Although it has been established that depression is related to dementia development, several studies to date have shown that depression does not have a role in the progression of MCI to dementia.[40,41]

COGNITION AND NEGATIVE HEALTH OUTCOMES

While there are several possible negative health outcomes that can be studied, this thesis focuses on the outcomes of mortality, dementia, vascular events, dependency, and hospitalization. The outcomes of dementia, dependency, and hospitalization highlight the societal and individual level impact of cognitive impairment, while the outcomes of mortality and vascular events highlight the individual impact of cognitive impairment.

Mechanisms behind the increased risk of negative health outcomes

There are several mechanisms that may explain why persons with CI may experience negative health outcomes. Firstly, CI could directly impact the ability of a person to comply with medications prescribed, thereby increasing their risk of negative health outcomes (Figure 2a). Similarly, CI could directly impact the ability of a person to alter their lifestyle and exercise habits, again increasing the risk of negative health outcomes. The direct effects of CI on compliance to prescribed medications and the ability to alter one's lifestyle are potentially modifiable by better caregiver training or innovative pharmaceutical devices. However, no studies to date have examined the relationship between CI and medication use and compliance. As a recent expert panel[42] has concluded that there are currently no modifiable factors to prevent AD or cognitive decline, the identification of modifiable risk factors may improve outcomes in high risk populations.

A second possible mechanism that may explain why persons with CI may experience negative health outcomes is that the same underlying disease process (e.g. atherosclerosis or neurodegeneration) that contributes to the development of CI may similarly contribute to the development of negative health outcomes (Figure 2b). As genetic and environmental factors that contribute to common diseases are usually shared by members of the same family, familial studies may be able to study the determine if the relationship between CI and negative health outcomes are due to underlying disease processes.

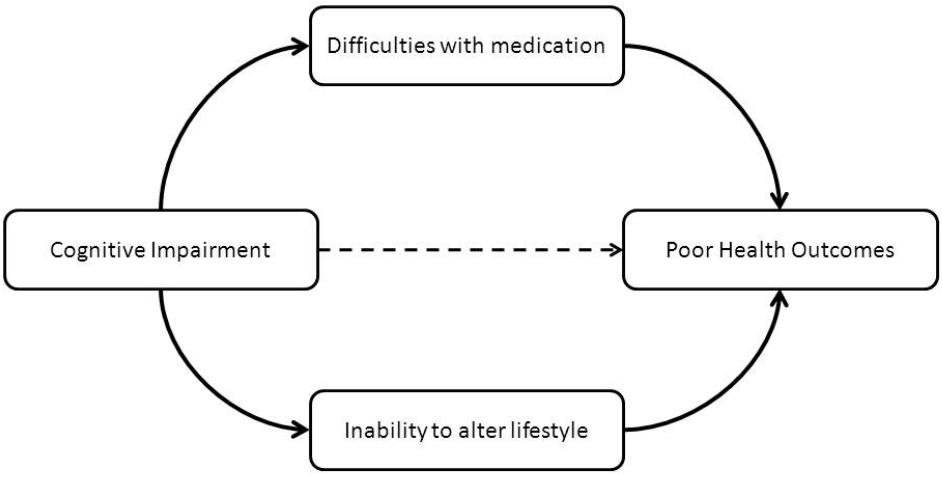

Figure 3a: Cognitive Impairment causes poor health outcomes via difficulties with medication or inability to alter lifestyle

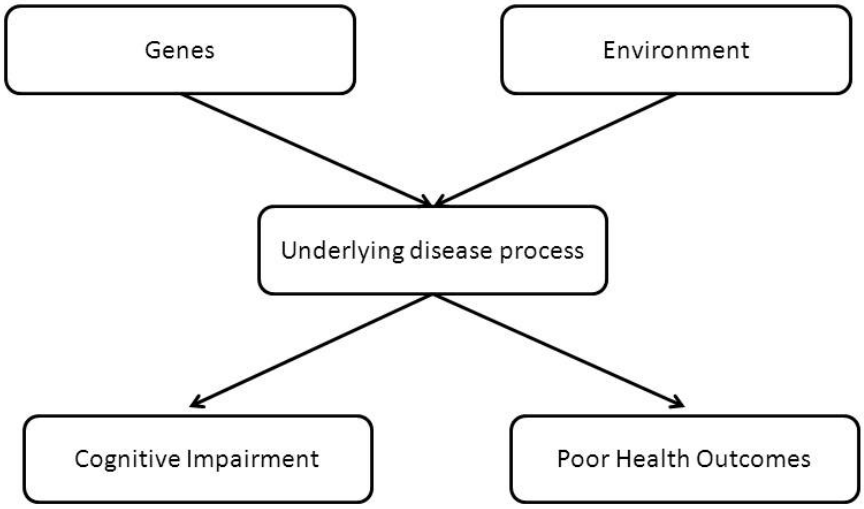

Figure 3b: Cognitive Impairment and poor health outcomes cause by the same underlying disease process

Stroke patients – A high risk subgroup

Stroke patients often have an overall poor prognosis, with approximately a third of stroke patients dying and a third becoming dependent within the first year after the index stroke[43]. This may be particularly important in ischemic stroke patients, as they are likely to have more vascular co-morbidities than their healthy counterparts [44]. PSCI may be a manifestation of the extent of cortical damage associated with the initial stroke. This damage can be directly due to cell death related to the ischemia during the stroke, or it may be due to inflammatory response to the ischemia. Stroke

patients therefore are a high-risk subgroup of the general population that is likely to experience negative health outcomes.

Medication use and dementia

As an increasing number of studies have demonstrated that cardiovascular risk factors are associated with an increased risk of dementia[45], recent studies have examined the effect of cardiovascular medication use on risk of dementia. Several large cohort studies have now shown that use of cardiovascular medications, particularly antihypertensive and lipid-lowering agents, reduces the risk of dementia[46,47]. However, no studies to date have examined whether persons with CI are receiving more or less cardiovascular medications when compared to their unimpaired counterparts.

On the other hand, little is known about the effect of antidepressant therapy on the risk of dementia. While clinical trials [48] have estimated the efficacy of antidepressant therapy in ameliorating depressive symptoms in AD or CI patients, only one study has examined the effect of antidepressant therapy on the risk of dementia. In that study, using population based inpatient, outpatient, and prescription medication registers, the study authors were able to show that use of antidepressant therapy increases the risk of dementia. However, as the study was a register-based study, they were unable to control for depression or cognitive status.

TWIN METHODS

Twin studies provide a good framework to study the underlying influences of genes and familial environment on a disease process. Fundamental to twin studies is the assumption that dizygotic twins (twins from two different fertilized eggs) share approximately 50% of their genetic information and 100% of the familial environment while monozygotic twins (twins from the same fertilized egg) share 100% of both their genetic information and their familial environment. Therefore, if genetic factors influence a particular disease, it is likely that both twins (concordance) in a monozygotic pair will have the disease more often than both twins in a dizygotic pair. Conversely, one can conclude that genetics is less important in the development of a

disease if both monozygotic and dizygotic pairs have similar rates of disease concordance.

3 AIMS

I. To identify ischemic stroke patients who are at highest risk for conversion to dementia based on CIND severity and MCI subtypes (Study I)

II. To determine if CIND and CIND severity predicts vascular events, dependency, and death in ischemic stroke patients (Study II)

III. To determine if CIND, SCI, and difficulties with medication predict dementia, hospitalization, vascular events, and death in a general population and whether these associations are confounded by genetics and shared environment. (Study III)

IV. To determine if cardiovascular and antidepressant medication influence the development of dementia in the general population and if the prescription patterns of cardiovascular and antidepressant medications are associated with cognitive status (Study IV)

4 MATERIALS AND METHODS

DATA SOURCES

In this thesis, the data used in Studies I and II are derived from Singapore, while the data used in Studies III and IV are derived from Sweden. Studies I and II are based on a cohort of ischemic stroke patients who were enrolled at one center of a multi-centric randomized controlled trial. In contrast, Studies III and IV are based on a study of dementia in the Swedish elderly (HARMONY)[49], which aimed to completely ascertain dementia in twins 65 years and older.

Studies I and II

The Stroke Group at the Singapore General Hospital Campus of the National Neuroscience Institute, a tertiary hospital, recruited non-disabled ischemic stroke and Transient Ischemic Attack patients for the European Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT-main)[50] between 1999 and 2005. Patients with a score of less than or equal to 3 on the modified Rankin Scale (MRS)[51] were considered non-disabled (Table 3).

MRS Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Table 3: Modified Rankin Scale

The ESPRIT-main trial was a two-armed trial in which patients with no contraindications to anticoagulation therapy (age>75, moderate to severe leukoariaosis, contraindications to warfarin therapy) were enrolled in Arm A and were randomized to warfarin, aspirin, or aspirin plus dipyridamole. Patients with any

contraindications to warfarin therapy were enrolled in Arm B, in which patients were randomized to aspirin or aspirin plus dipyridamole.

Patients recruited into the ESPRIT-main study were eligible to enter the cognitive substudy, ESPRIT-cog, if they did not have any of the exclusion criteria for the cognitive substudy. The exclusion criteria for the cognitive substudy were confusion, severe aphasia (expressive or receptive), major psychoses diagnosed according to Diagnostic and Statistical Manual of Mental Disorders- 4th Edition (DSM-IV) criteria[52], or dominant upper limb paralysis. Patients who consented to enroll in the ESPRIT-cog substudy received their baseline cognitive assessment three months after their qualifying event and were followed up with annual neuropsychological assessments for up to five years.

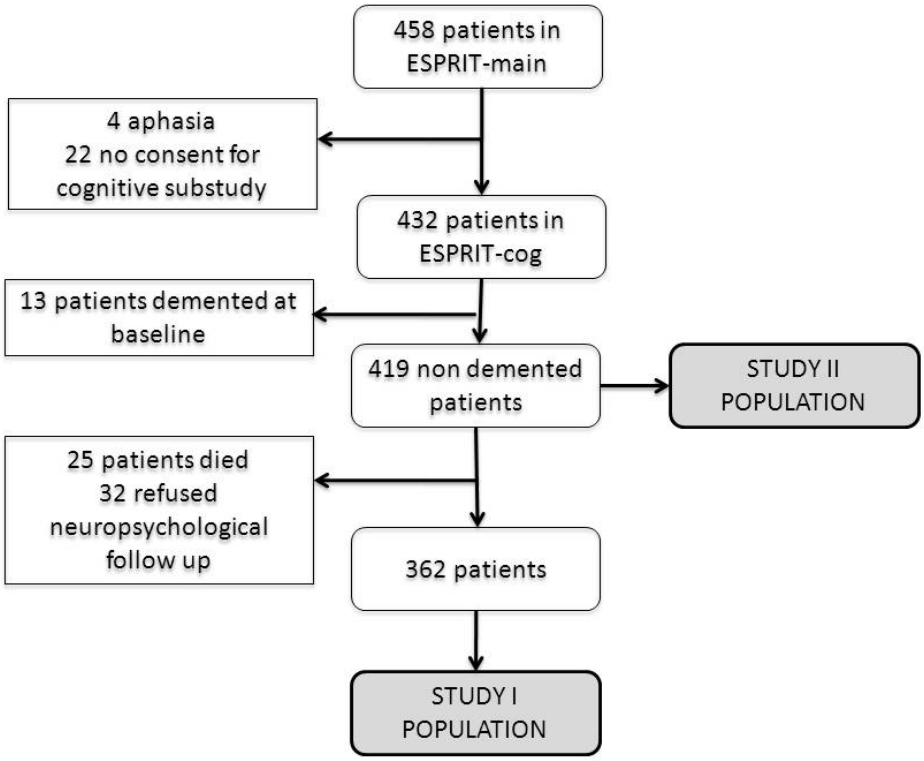

Figure 4: Study population of Studies I and II

Figure 4 summarizes the patient population of Studies I and II. Briefly, 458 patients were recruited into ESPRIT-main, of which 432 enrolled in the cognitive substudy. As Study I required follow-up neuropsychological testing, only the 362 patients with no dementia at baseline and at least 1 follow up neuropsychological visit were included. All 419 non-demented patients were included in Study II regardless of neuropsychological follow up status.

Studies III and IV

Participants in Studies III and IV were part of HARMONY, a study which derived its participants from the Swedish Twin Registry (STR)[53], a population based register that comprises over 170,000 Swedish twins born after 1886. Detailed methodology of HARMONY has been described elsewhere[49]. Briefly, all members of the STR aged 65 and above were screened for cognitive impairment in a 2.5-year period beginning March 1998 (screening phase). Participants who were suspected of cognitive impairment, their twin partners, and a subset of cognitively intact controls were invited for a clinical workup (clinical phase) in which dementia status was ascertained. All participants who were deemed to have dementia or "questionable dementia" during the clinical phase were excluded from this study.

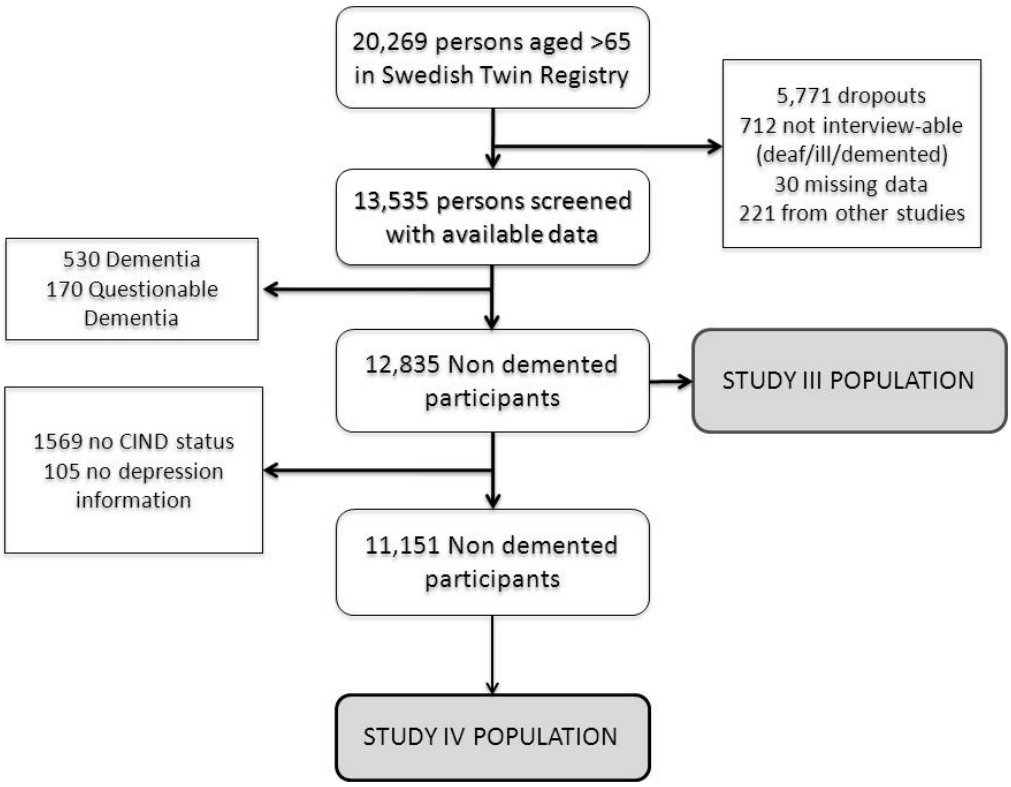

Figure 5: Study population of Studies III and IV

Figure 5 summarizes the patient population of Studies III and IV. Briefly, 20,269 persons aged 65 and above at baseline were eligible for inclusion in HARMONY. Of these 20,269 persons, 5,771 were not contactable, 712 were contactable but not interviewable, 30 had missing data, and 221 were recently seen in other studies, resulting in a total of 13,535 persons with screening information. Of these, 530 were found to have dementia and a further 170 had "questionable" dementia, leaving

12,835 non-demented participants. These 12,835 participants made up the study population in Study III. However, as information from the telephone screen alone (and not the informant reports) was used to derive the CIND status, persons with inadequate answers to the telephone screen had no CIND status and were therefore excluded from Study IV. Therefore, the 1,569 persons with no CIND status and the further 105 persons with no depression information were excluded from Study IV, resulting in a study population of 11,151 in Study IV.

NEUROPSYCHOLOGICAL TESTING

Studies I and II

Neuropsychological Test Battery

The neuropsychological test battery that was administered in Studies I and II consisted of six domains, two memory domains, and four non-memory domains. Education adjusted cutoffs of 1.5 standard deviations below established normal means were used on individual tests. Failure in at least half of the tests in a domain constituted failure in that domain. The assessment was administered in English, Malay, Mandarin, or Chinese dialects according to the subject's habitual language. The entire battery took under an hour and a half to complete. The lists of tests used in each domain are detailed below in Table 4.

Derivation of CIND and MCI statuses

Patients with CIND were impaired in at least one domain of the neuropsychological test battery, but did not meet criteria for dementia[4]. On the basis of the sample median, CIND was divided into CIND-mild (1-2 domains impaired) and CIND-moderate (3-6 domains impaired). Patients were also classified by MCI subtypes (amnestic single-domain MCI, non-amnestic single domain MCI, multiple domain MCI with an amnestic component, and non-amnestic multiple domain MCI) according to the revised MCI criteria[29]. Since all patients with CIND had cognitive complaints, there were no patients with CIND who did not meet the criteria for MCI. Additionally, to facilitate the comparison between CIND and MCI, both definitions used cutoffs of 1.5 standard deviations below education-adjusted means.

Domain	Neuropsychological Tests
Attention	Digit Span Forwards and Backwards[54], Visual Memory Span Forwards and Backwards[54], Auditory Detection[55]
Language	Modified Boston Naming Test[56], Verbal Fluency Test (Animals and Food subtasks)[57]
Verbal Memory	Word List Recall (Immediate, Delayed, Recognition)[58], Story Recall (Immediate and Delayed)[54]
Visual Memory	Picture Recall (Immediate, Delayed, Recognition)[54], WMS-R Visual Reproduction (Immediate, Delayed, Recognition)[54]
Visuoconstruction	WMS-R Visual Reproduction (Copy)[54], Clock Drawing, WAIS-R Block Design[59]
Visuomotor Speed	Digit Cancellation Task[60], Digit Symbol Modalities Test[61], Maze Task[62]

Table 4: Domains in the neuropsychological test battery

Studies III and IV

Screening phase

Cognitive Screening was performed over the telephone with the TELE cognitive screening instrument [63,64]. The TELE consists of a 10-item mental status questionnaire (MSQ), three other cognitive domains (three word recall, three word pair similarities, counting backwards in threes), and questions about health and daily functioning. The TELE also includes a section investigating cognitive complaints, including a general question investigating subjective cognitive change "Have you noticed any change in your memory during the last three years?". For participants who were impaired on the TELE, an informant was interviewed with the Blessed Dementia Rating Scale (BDRS)[65]. The TELE and BDRS were then combined into an ordinal scale (ORD) with scores ranging from 0 (cognitively intact) to 3 (cognitively impaired). The following are examples of what constituted an ORD score of 3: More than 3 errors on the MSQ; functional impairment in activities of daily living due to memory impairments; failed one third of the items on the TELE or impaired in 2 domains of the MSQ with a BDRS of at least 1.5. These are based on established cutoffs for functional impairment[65].

Clinical Phase

Individuals with an ORD score of 3 were referred for clinical workup. If the individual was suspected of dementia, his or her twin partner was invited for clinical workup regardless of screen status. Additionally, a sample of 35 normal control twin pairs in which both twin members screened negative were included in the clinical phase. The clinical phase comprised of physical and neurological examinations, neuropsychological evaluations including screening for depression, biochemical evaluations, as well as referrals for neuroimaging. Clinical diagnoses of dementia were made in consensus conferences based on the above information in accordance to the DSM-IV criteria[52]. An additional category of "questionable dementia" was added for individuals who did not fulfill one of the three DSM- IV diagnostic criteria, but did exhibit at least two of the criteria: memory problems, problems in another area of cognition, or functional impairments.

Derivation of CIND, SCI, and Depression status

Participants were classified as having CIND if they performed two standard deviations below the age and education adjusted means in any of the four cognitive tasks in the TELE but did not fulfill the criteria for dementia[4]. Participants were classified as having SCI if they responded positively to the following question "Have you noticed any change in your memory during the last three years?" Participants were classified as having had depression if they fulfilled four or more criteria on the International Diagnostic Interview Short Form adapted to asses lifetime major depression[66,67], or had a score of eight points or above on the eleven item version of the Center for Epidemiologic Studies Depression scale[68].

OUTCOME ASCERTAINMENT

Studies I and II

Dementia

In order to exclude persons with dementia at baseline in Studies I-IV, consensus conferences that considered neuropsychological, clinical, neurological, biochemical, and imaging studies were considered. Dementia was diagnosed according to the DSM-IV criteria. In Study I, the same criteria are applied to derive the outcome of dementia.

Dependency, Death, and Vascular Events

In Study II, information pertaining to dependency and vascular events were ascertained at either at clinic visits or at 6 monthly telephone calls. Dependency was measured by the MRS[51], and was dichotomized into good outcome (0-2) and bad outcome (3-6). Patients with a MRS of 3 at baseline were considered dependent only if they progressed to MRS scores >3. If a recurrent vascular event had occurred, detailed hospital records were obtained to verify the occurrence of the vascular event. Strokes, peripheral artery disease, intracranial bleeds, and any cardiac ischemia (stable and unstable angina, myocardial infarctions) or deaths from any of the above were considered to be a recurrent vascular event. Information pertaining to death was collected either verbally and confirmed with hospital and/or death registry records at the end of the study.

Studies III and IV

In Studies III and IV, outcomes were ascertained through the linkage of population-based registers to the Swedish Twin Registry. The National Patient Register (NPR)[69] covers all hospital discharges in Sweden since 1987 (with partial coverage since 1964) and the Cause of Death Register (CDR)[70] covers all deaths since 1961. At the time of the study the NPR was available until the end of 2009 and the CDR was available until the end of 2008. In the registers, the primary cause of hospitalization or underlying cause of death is recorded in addition to up to 6 contributory causes in the NPR and up to 20 contributory causes in the CDR. Diagnoses are recorded with the Swedish versions of International Classification of Diseases (ICD) codes. The major difference between the Swedish and the international version of ICD is that in ICD9 the last character of the code is a letter instead of a number. The equivalents are as follows: 0=A, 1=B, 2=C, 3=D, 4=E, 8=W, 9=X. The list of ICD codes that were used to identify dementia and vascular events are summarized below in Table 5.

Dementia and vascular events were ascertained through the combination of the NPR and CDR. Only about half of all dementia cases are captured in the registers since hospitalization or death due to dementia as the primary cause is relatively uncommon. The specificity and positive predictive value of dementia diagnoses are close to 100%[71]. Previous validation studies have shown capture is much better with

vascular events such as stroke and myocardial infarctions[72,73]. Hospitalization was ascertained through the NPR and death was ascertained through linkage with the Swedish Population Register, for which data was available until the end of 2010.

	ICD7	ICD8	ICD9	ICD10
Dementia				
Alzheimer's Disease	305,304	290	290A/B/X, 331A	F00, G30, F03
Vascular Dementia	306	293.0, 293.1	290E	F01
Other Dementia			294B, 290W, 331B/C/X	F02, G311, G318A, F051
Vascular Event				
Hemorrhagic Stroke	331	432-434	432-434	I61
Ischemic Strokes	332	431	431-432	I63
Transient Ischemic Attack	333	435	435	G45X, I66, G46
Myocardial Infarction or Unstable Angina	420	410-411	410-411	I21, I22
Stable Angina or Ischemic Heart Disease	420	412-414	412-414	I20, I24, I25

Table 5: ICD codes that are used in Studies III and IV. ICD= International Classification of Diseases

Information on the use of the cardiovascular medication was derived from the Prescription Drug Register (PDR)[74]. The PDR contains individual-based data for all prescriptions dispensed to the whole population of Sweden. We used information on medication use from the when the registry started on July 1st 2005 to July 1st 2009. In the registry, medications are categorized by the Anatomical Therapeutic Chemical (ATC) Classification system as recommended by the World Health Organization[75].

Antidepressants were identified by the ATC code N06A, and two different subtypes, tricyclic antidepressants (TCAs) with the ATC code N06AA, and Selective Serotonin

Reuptake Inhibitors (SSRIs) with the ATC code N06AB were identified. Cardiovascular mediations were identified by the following ATC codes: C01AA (digitalis), C03A (thiazide diuretics), C03C (loop diuretics), C03D (potassium sparring diuretics), C07A (beta blockers), C08 (calcium channel blockers), C09A (Angiotensin Converting Enzyme inhibitors), C09C (angiotensin II inhibitors), and C10A (lipid lowering agents). For subtypes of cardiovascular medication, we combined all the antihypertensives into one subtype (thiazide, loop, and potassium sparring diuretics, calcium channel blockers, ACE inhibitors, and angiotensin II antagonists), and considered digitalis, beta-blockers, and lipid lowering agents as separate subtypes. Medication use was stratified into intervals of 6 months corresponding to the 1st and 2nd halves of each calendar year.

STATISTICAL ANALYSIS

All statistical analyses were performed with the statistical package STATA[76], with versions 10.0 used in Studies I and II and 11.0 used in Studies III and IV.

Logistic models are commonly used to study the effect of predictor variables on categorical outcomes. While logistic models are used in Study III, the majority of the analyses in this thesis use Cox proportional hazards models.

Cox Regression Analyses

The Cox Proportional Hazards models are one form of survival analysis. In survival analysis models, instead of the traditional dichotomous (yes/no) outcome seen in logistic models, the model is based on time to event. The time to event among the cases is the time passed between baseline and the outcome. For non-cases who do not experience the outcome, the time contributed to the analyses is calculated as the time passed from baseline to either death, loss to follow-up, or end of study. In survival analysis, the main effect measure is the Hazards Ratio (HR). The HR is defined as the hazards in the exposed group divided by the hazards in the unexposed group. The Cox proportional hazards model is a semi-parametric model, which means that the baseline hazards function (i.e. the shape of the underlying survival curve) does not have to be specified, as it would be in a fully parametric model.

Twin Analyses

One of the fundamental assumptions that most analytical models is that the persons in the analyses are independent of one another. In twin studies, this assumption is violated. Thankfully, there are several approaches to model the underlying correlation between the twins in order to use the conventional models without violating these assumptions.

General Estimating Equations (GEE) is an iterative method in which different statistical weights are assigned to each cluster (in this case, twin pair). These weights are then used to calculate the variance, covariance, and correlations in the sample. The estimated correlation is then used to re-estimate the weights in the next cycle. This process is repeated until the estimates stabilize. Once stabilized, the final estimate of the correlation is used to estimate the standard error. In most cases, the use of GEE will increase the standard errors while leaving the estimates unchanged. GEE is used to correct for the clustering due to the presence of twins in Studies III and IV.

Another method of controlling for the underlying correlations in twins is to perform matched analyses. Conditional logistic regression is used to analyze matched data, and when used with twin data, is commonly referred to as either co-twin control analysis or within-pair analysis.

STUDY DESIGNS

Figure 6 summarizes the study designs of the four studies in this thesis. Briefly, all studies included in this thesis had a cohort design. Studies I and II were based on a cohort of Singaporean stroke patients while Studies III and IV were based on a cohort of Swedish twins.

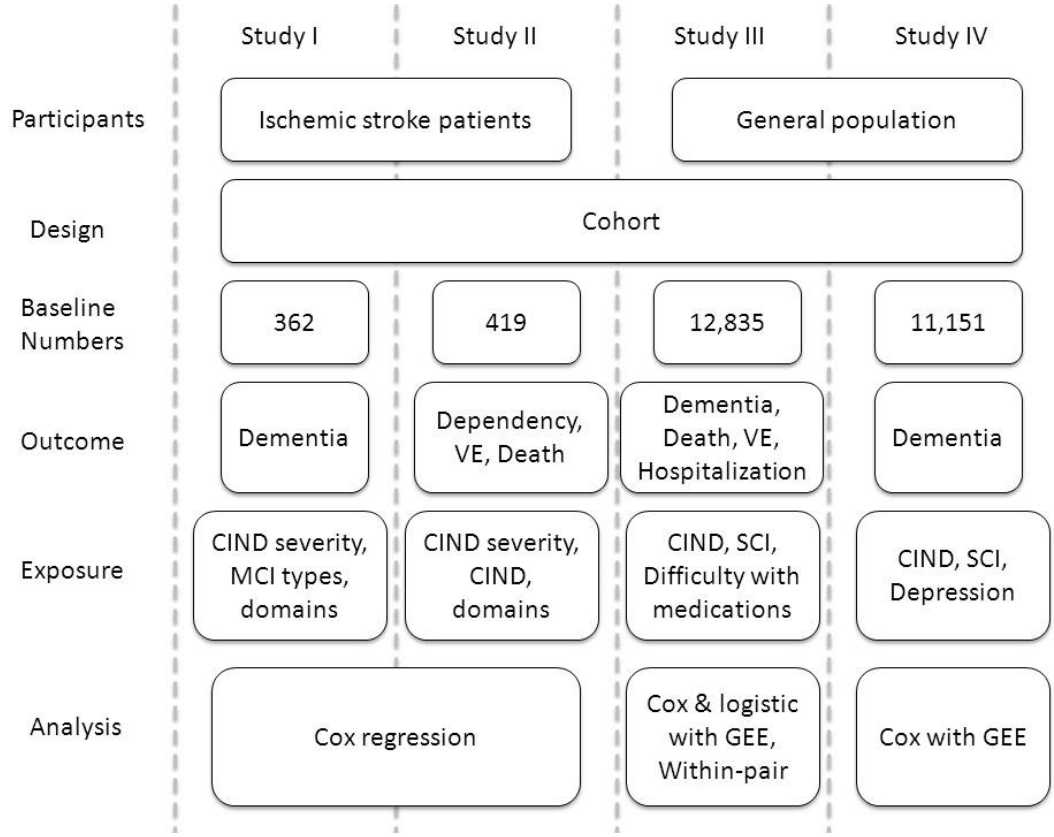

Figure 6: Summary of study designs used in Studies I – IV. Abbreviations: VE= Vascular Events, CIND = Cognitive Impairment No Dementia, MCI = Mild Cognitive Impairment, SCI = Subjective Cognitive Impairment, GEE = General Estimating Equations

Study I: Severity of CIND versus MCI subtypes in predicting dementia

In Study I, we aimed to determine whether CIND severity predicted dementia among post-stroke patients. We also aimed to compare CIND and MCI subtypes as predictors of dementia. Lastly, we also assessed the ability of cognitive domains to predict dementia. These aims were evaluated in a cohort of 362 ischemic stroke patients who were recruited at the Singapore General Hospital between 1999 and 2005. CIND severity (CIND-mild and CIND-moderate), MCI subtypes, and the 6 cognitive domains were the main exposures of interest.

In addition to the main exposures of interest, the following covariates were examined for their association with incident dementia: age, gender, stroke subtype, diabetes mellitus, hypertension, smoking, recurrent stroke during study follow up, baseline MRS score, baseline mini-mental state examination score, and previous vascular events (stroke, myocardial infarct, angina, ischemic heart disease, or peripheral artery disease). Information on these covariates was determined at baseline from a combination of self-report and medical records.

Univariate Cox regression analyses were performed to identify significant predictors of incident dementia. Exposures that were significant in the univariate stage were included in multivariable analyses that controlled for treatment allocation. The exposures of interest were entered into separate regression models due to colinearity. Significance was determined with a two-tailed alpha of 0.05 in analysis of CIND severity and MCI subtypes while Bonferroni adjustment for multiple comparisons yielded an alpha of 0.008 for domain analyses. Lastly, uniform scores were derived for each domain and averaged across the patients in different MCI and CIND severity, after which receiver-operating curves were plotted to compare the area under curve of the different classifications.

Study II: CIND, CIND severity and negative health outcomes

In Study II, we aimed to determine whether CIND severity predicted negative health outcomes other than dementia among post-stroke patients. The specific outcomes of interest were dependency (MRS>3), vascular events, and death. Furthermore, we aimed to determine if specific domains of cognitive impairment could predict these outcomes. These aims were evaluated in a cohort of 419 ischemic stroke patients who were recruited at the Singapore General Hospital between 1999 and 2005. CIND, CIND severity (CIND-mild and CIND-moderate), and the 6 cognitive domains were the main exposures of interest.

In addition to the main exposures of interest, the following covariates were examined for their association with negative health outcomes: age, gender, stroke subtype, diabetes mellitus, hypertension, smoking, recurrent stroke during study follow up, baseline MRS score, baseline mini-mental state examination score, and previous vascular events (stroke, myocardial infarct, angina, ischemic heart disease, or peripheral artery disease). Information on these covariates was determined at baseline from a combination of self-report and medical records.

Univariate Cox regression analyses were performed to identify significant predictors of negative outcomes. Exposures that were significant in the univariate stage were included in multivariable analyses that controlled for treatment allocation. The

exposures of interest were entered into separate regression models due to colinearity. Significance was determined with a two-tailed alpha of 0.05 in analysis of CIND and CIND severity while Bonferroni adjustment for multiple comparisons in domain analysis yielded an alpha of 0.008.

Study III: Why does Cognitive Impairment lead to negative health outcomes?

In Study III, we aimed to determine the reasons why persons with CIND or SCI experience negative health outcomes. Specifically, we wanted to ascertain whether difficulties with medication or underlying genetic and environmental factors were associated the development of negative health outcomes of dementia, death, hospitalization, and vascular events. These aims were evaluated in a cohort of 12,835 non-demented Swedish twins who were evaluated for cognitive status as part of a population based study, HARMONY.

The main exposures of interest, CIND and SCI, were entered into separate models. In order to examine whether difficulties with medication affected negative health outcomes, an indicator of having difficulties with medication was also entered into yet another model. To determine whether difficulties with medication modified the association between negative health outcomes and CIND or SCI, the indicator of difficulties with medication was also entered in the same model as CIND or SCI. The indicator of difficulties with medication was derived from a self-reported answer to the question “Have you had problems with taking your medication”.

In addition to the main exposures of interest, all multivariable models adjusted for age, gender, and education. Additionally, models that predicted dementia controlled for previous strokes while models that predicted death and vascular events controlled for previous vascular events. Multivariate regression analyses were performed in three different ways: 1) Cox Regression Analysis with GEE adjustments; 2) Logistic Regression Analysis with GEE adjustments; and 3) Co-twin controlled Conditional Logistic Regression Analysis in which twins discordant for both cognitive status and outcome are analyzed in a matched case-control fashion in MZ Twins (within-pair analysis). To determine whether genetics and shared environment modified the relationship between negative health outcomes and CNID or SCI, estimates from the

logistic regression analyses were compared with estimates from the within-pair analyses.

In this study, we included both Cox and Logistic models with GEE as we believed that in certain outcomes, time to failure may be more important than failure. However, as the Cox regression analyses with GEE adjustments are not directly comparable to the conditional logistic regression analyses in the within-pair analyses, we chose to include logistic regression analyses with GEE adjustments. In the within-pair analyses, pairs in which the control twin was not alive when his or her partner became demented, was hospitalized, or experienced a vascular event were excluded from the analyses.

Study IV: Medication use and dementia

In Study IV, we aimed to determine whether use of antidepressant or cardiovascular medications were associated with dementia. We also aimed to evaluate whether use of antidepressant or cardiovascular medication changed the association between dementia and either CIND, SCI, or depression. Lastly, we aimed to determine if individuals with CIND, SCI, or depression received more antidepressant or cardiovascular medications compared to their unimpaired counterparts. These aims were evaluated in a cohort of 11,151 non-demented Swedish twins who were evaluated for cognitive status as part of a population based study, HARMONY. Of these 11,151, only 9,112 were alive and non-demented at the start of the PDR.

The main exposures of interest were CIND, SCI, depression, use of any antidepressant medication, and use of any cardiovascular medication. Medication use (dichotomous) was considered a time varying exposure. Multivariable analyses were performed using Cox Regression Analyses in three stages. In the first stage, CIND, SCI, and depression were entered in separate multivariable models that controlled for age, education, gender, and previous stroke. In the second stage, the models from stage one were adjusted for use of any antidepressant medications or cardiovascular medications. In the third stage of analysis, subtypes of antidepressant medications (SSRIs and TCAs) and cardiovascular medications (antihypertensives, beta blockers, digitalis, and lipid-lowering agents) were added into the models from stage one. Lastly, the Mann

Whitney U test was used to compare the number of prescriptions (ordinal) for antidepressant or cardiovascular medication by CIND, SCI or depressive status.

5 RESULTS AND DISCUSSION

Study I: Severity of CIND versus MCI subtypes in predicting dementia

Study I aimed to determine whether CIND severity predicted dementia in ischemic stroke patients and whether CIND severity or MCI subtypes were better at predicting dementia.

Of the 362 patients (mean age 60 ± 11 years, 30% women) in this study, 179 (49%) had cognitive impairment at baseline. In terms of CIND severity, 94 patients had CIND-mild while 85 had CIND-moderate. In terms of MCI subtypes, 20 had single domain amnestic MCI, 33 had single domain non-amnestic MCI, 99 had multiple domain amnestic MCI, and 27 had multiple domain non-amnestic MCI. The proportion of patients with cognitive impairment was larger than expected considering that only persons with non-disabling stroke were involved in this study. Previous studies have shown that the prevalence of post stroke CIND ranges from 20% to 79%[24,33,77,78]. This range is particularly wide due to differences in study design, particularly with regards to the time point chosen in relation to the time of stroke. As most of the cognitive recovery occurs within 3 weeks to 3 months after a stroke[79], studies that measure cognitive status closer to the onset of stroke tend to find a higher prevalence of post stroke CIND.

During the course of the study, 24 patients converted to dementia. The incidence of dementia in patients with no impairments at baseline was 11 per 1,000 while the incidence of dementia in patients with CIND-mild and CIND-moderate were 42 per 1,000 and 212 per 1,000 respectively. In multivariable analyses, the risk of incident dementia for persons with CIND-mild was not significantly different from those with no impairments (HR 1.04, 95% Confidence Interval (CI) 0.17-6.37). However, those with CIND-moderate were at six times increased risk of incident dementia (HR 6.43 95% CI 1.30-31.7). Therefore CIND severity was able to discriminate those at high risk of dementia from those who were not at high risk. While previous studies have stratified CIND subtypes based on etiology, no studies have attempted to stratify CIND into subtypes based on severity.

The incidence rates of dementia in the various MCI subtypes were as follows: 50 per 1,000 in amnestic single domain MCI, 30 per 1,000 in non-amnestic single domain MCI, 181 per 1,000 in multiple domain amnestic MCI, and 71 per 1,000 in multiple domain non-amnestic MCI. In multivariable analysis, the risk of incident dementia was significantly increased in only the multiple domain amnestic MCI subtype (HR 5.77 95% CI 1.19-28.0). Comparisons between CIND severity and MCI subtypes showed that CIND-moderate is not significantly better than multi-domain amnestic MCI in predicting incident dementia. However, since memory impairments are more relevant in populations at risk for AD, and as stroke populations are more likely to convert to VAD or mixed dementia rather than AD, CIND severity may be a more appropriate measure than MCI subtypes in a post stroke setting. Fourteen percent of patients with CIND moderate only, 4% of patients with multiple domain amnestic MCI only and 17% of patients with both CIND moderate and multiple domain amnestic MCI converted to dementia.

In multivariable domain specific analysis, visual memory (HR 6.92, $p<0.001$) and verbal memory (HR 4.25, $p=0.002$) were significant predictors of dementia. These findings were in agreement with previous stroke studies that have shown that verbal memory was more likely to deteriorate in ischemic stroke patients who convert to dementia[80]. However, it is unclear whether this result is an artifact due to the requirement of memory impairment for the diagnosis of dementia.

Study II: CIND, CIND severity and negative health outcomes

Having shown that CIND severity discriminates those at high risk of dementia from those at low risk of dementia in a post stroke setting, we aimed to determine whether CIND severity discriminates those at high risk for negative health outcomes in the same population.

Of the 419 patients in this study, 207 (49%) of patients had CIND (109 (26%) with CIND-mild and 98 (23%) with CIND-moderate) at baseline. During the course of the study, 28 patients died, 62 had a vascular event, and 48 became dependent. The

incidence of death, vascular events and dependency by baseline cognitive status is summarized in Table 6.

	Death	Vascular events	Dependency
No impairments	0.2	1.0	0.3
CIND-mild	0.9	1.8	1.9
CIND-moderate	1.4	2.1	2.2

Table 6: Incidence rates per 1,000 person years

In multivariable analyses, patients with CIND were at an increased risk of dependency (HR 3.77 95% CI 1.53-9.37), but CIND severity was unable to discriminate between those at high and low risk of dependency, as patients with both CIND-mild and CIND-moderate were an increased risk of dependency. Additionally, in domain specific analyses, impairments in visuomotor speed predicted dependency. These findings were in agreement with previous studies in stroke patients that have shown that visual perception and constructional difficulties independently predict disturbances in instrumental activities of daily living[81].

We also found that patients with CIND were at increased risk of death (HR 3.27 95% CI 1.06-10.1) as compared to those without impairments. Furthermore, CIND severity was able to discriminate between those at high and low risk of death, with persons with CIND-moderate at approximately four times the risk of death (HR 3.81 95 %CI 1.13-12.8) as compared to unimpaired persons. However, there were no independent cognitive domains that predicted death.

However persons with CIND were not at an increased risk of vascular events as compared to unimpaired persons. Similarly, CIND severity and domain specific impairments showed no association to the risk of vascular events. These results were unexpected since we had hypothesized that persons with CIND would be less compliant to medication regimens and lifestyle changes. However, in the Singaporean context, as elderly persons live within family units as opposed independently, factors such as forgetting medication and apathy to lifestyle changes may have less of an

impact on the patient's health than in other countries. The association between CIND and vascular events (HR 1.67 CI 0.93-3.00) improved, but remained non significant when analyses was restricted to those with fatal vascular events (HR 1.73 CI 0.61-5.02) suggesting that another possible explanation for the lack of significant association between CIND and vascular events is that we may have been underpowered to detect a significant effect on vascular events.

Study III: Why does Cognitive Impairment lead to negative health outcomes?

The main aim of Study III was to test two possible hypotheses that attempt to explain why persons with CIND and SCI have negative health outcomes. The first hypothesis involved persons with CIND and SCI having more difficulties with medication and therefore experiencing worse outcomes. The second hypothesis was that the underlying genetic and shared environmental factors in twins would explain the association between CIND and negative health outcomes.

	Cohort Analyses			DZ only			MZ only		
	OR	95% CI		OR	95% CI		OR	95% CI	
ORD 0	1.00	- -		1.00	- -		1.00	- -	
ORD 1	**1.52**	**1.27**	**1.81**	1.27	0.83	1.92	1.07	0.53	2.15
ORD 2	**2.25**	**1.78**	**2.59**	**1.83**	**1.03**	**2.66**	0.62	0.22	1.80
ORD 3	**3.36**	**2.72**	**4.15**	**2.11**	**1.39**	**3.34**	1.11	0.37	3.39
no CIND	1.00	- -		1.00	- -		1.00	- -	
CIND	**1.73**	**1.48**	**2.01**	**1.38**	**1.01**	**2.09**	1.03	0.45	2.35
no SCI	1.00	- -		1.00	- -		1.00	- -	
SCI	**1.69**	**1.44**	**1.99**	**3.01**	**1.86**	**8.19**	**3.17**	**1.22**	**11.67**

Table 7: Associations between cognitive exposures and odds of dementia in cohort analyses and within pair analyses in DZ and MZ twin7s

In the 12,835 non-demented twins in this study, 993 developed dementia (314 within the first 5 years). In multivariable analyses, CIND (OR 1.73 95% CI 1.48-2.01) and SCI (OR 1.69 95% CI 1.44-1.99) were significant predictors of dementia. In within-pair analyses in MZ twins only, SCI remained a significant predictor of dementia (OR 3.17 95% CI 1.22-8.22) but CIND was no longer associated with dementia (OR 1.03 95% CI 0.45-2.35), suggesting that much of the association between CIND and dementia can be explained by genetics and shared environmental factors. Analyses with DZ twins showed results in between that of MZ twins and cohort analyses (Table 7), suggesting that genetics are more likely to explain the association between CIND and dementia

than environment. Difficulties with medication predicted time to dementia (HR 2.49 95% CI 1.58-3.92) but when added into models that tested the association between dementia and either CIND or SCI, did not modify the estimates. This suggests that while difficulties with medication are associated with time to dementia, the effect of difficulties with medication on dementia is independent of CIND or SCI. The conceptualized associations between CIND, SCI, difficulty with medication, and dementia can be summarized in Figure 7.

To our knowledge, no studies have previously attempted to elucidate the mechanisms behind the progression of CIND and SCI to dementia. Taken together, our results suggest that while difficulties with medication may be one mechanism by which persons increase their risk of dementia, other mechanisms, particularly genetic and shared environmental factors, may be more important in the progression of CIND to dementia. Since we are not be able to change a person's underlying genetic risk, CIND can be considered a marker of the underlying genetic risk. However, as difficulties with medication is an independent risk factor for dementia, persons at high risk of dementia (i.e. persons with CIND) should be offered tools by which they may be able to reduce medication errors, thereby possibly delaying the onset of dementia. One possible mechanism would be to enable elderly persons to access their medication using multi-dose drug dispensing methods such as Sweden's "Apodos" system[82].

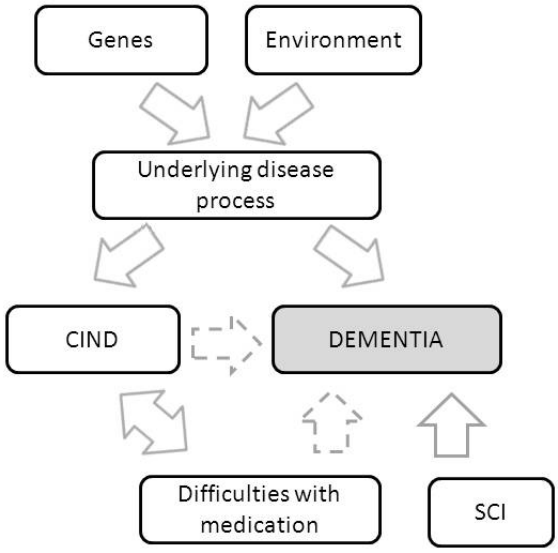

Figure 7: Conceptualized associations between CIND, SCI, difficulties with medication and dementia

One of the more clinically relevant findings in this study was the increased risk of dementia associated with SCI, which was not explained by genetic and environmental factors. The increased risk of dementia was present in those with SCI regardless of CIND. These results confirm the results from previous studies that show that memory complaints are predictive of cognitive decline and dementia[83-86]. These results also suggest that it may be clinically useful for general physicians to ask the question "Have you noticed any change in your memory during the last three years" as a quick screen in order to identify persons at increased risk of dementia. However, this should not be a substitute for more extensive neuropsychological screening.

A total of 5,125 study participants died during the course of the study. As with dementia, CIND was predictive of mortality in cohort analyses (OR 1.43 95% CI 1.30-1.57) but not associated with mortality in within-pair analysis (OR 0.91 95% CI 0.57-1.43). Our finding that CIND predicts mortality confirms existing reports in the literature[5,34,87]. While some of the effects of CIND on mortality were explained by difficulties with medication, both CIND and difficulties with medication (OR 5.01 95% CI 3.26-7.71) were independent predictors of mortality. This suggests that the increased risk of mortality from having CIND may be both due to difficulties with medication use and due to the fact that CIND may be a marker for an underlying disease process.

In this study, we also found that both CIND (HR 1.10 95% CI 1.05-1.15) and SCI (HR 1.09 95% CI 1.04-1.13) predicted time to hospitalization. Comparison with other studies is difficult, as no previous reports have examined the association between CIND or SCI and hospitalization. However, one study found that persons with CIND are two and a half more times likely to get institutionalized in nursing homes as compared to persons with no cognitive impairment [5]. Additionally, as with Study II, we found no association between vascular events and SCI or CIND. The strongest predictor of having a vascular event was having already had a vascular event, which would further explain why we see no association between CIND severity and vascular events in stroke patients (Study II).

Study IV: Medication use and dementia

Study IV had three main aims: 1) to determine whether antidepressant or cardiovascular medications were associated with dementia; 2) to determine whether the use or antidepressant medication changed the association between dementia and CIND, SCI, or depression; and 3) whether individuals with CIND, SCI, or depression received more prescriptions for antidepressant or cardiovascular medications than their unimpaired counterparts.

Of the 11,151 persons in this study (whole cohort), 9,112 were alive and non-demented (restricted cohort) at the start of the PDR. In both whole and restricted cohort analyses, use of any antidepressant medication (HR 2.05 95% CI 1.59-2.79) doubled the risk of dementia. In analyses looking at the subtypes of antidepressants, SSRIs double the risk of dementia (HR 2.23 95% CI 1.55-3.21) while TCAs were not associated with dementia (HR 0.35 95% CI 0.05-2.46). However the use of antidepressants does not modify the association between dementia and SCI. Persons with CIND, SCI and depression all received more prescriptions for antidepressant medication than their unimpaired counterparts.

Our finding that SSRIs doubled the risk of dementia agrees with the only large population-based study that has evaluated the effect of antidepressant medication on dementia[88]. However, as their study was entirely registry based, they were not able to correct for cognitive or depressive status in their analyses as we do in this study. While antidepressant treatment has been shown to have a strong effect on severely depressed patients, recent meta-analyses indicate that there is a slight or negligible effect on persons with mild to moderate depression[89]. In light of these findings, and in light of the fact that late-onset depression may be a prodrome of dementia rather than a risk factor, one wonders whether the late-onset depression should be treated at all. While they may alleviate depressive symptoms, antidepressant use may tip an elderly person at high risk to manifest dementia. This is why it is particularly alarming that persons with CIND and SCI receive more antidepressant medication than their unimpaired counterparts.

In both whole and restricted cohort analyses, use of any cardiovascular medication (HR 0.56 CI 95% 0.45-0.70) halved the risk of dementia. In analysis looking at the subtypes of cardiovascular medications, only antihypertensive medication (HR 0.68 95% CI 0.51-0.89) and lipid-lowering agents (HR 0.48 95% CI 0.31-0.73) showed the same protective effect. However, the use of cardiovascular medications does not modify the association between dementia and CIND or SCI. Persons with CIND or SCI received significantly less prescriptions for cardiovascular medication than their unimpaired counterparts.

Our results that cardiovascular medications, particularly antihypertensives and lipid lowering agents, reduce the risk of dementia confirm the results of previous studies on the same subject [46,47]. However, the fact that persons with CIND and SCI receive less of these medications than their unimpaired counterparts is further cause for worry. Persons with cognitive impairment may not be as attentive or vocal in their interactions with their physicians, and these results suggest that physicians may need to pay closer attention to the overall medication regimens that their cognitively impaired patients are on.

6 LIMITATIONS

Study I

In studies I and II, the use of the ESPRIT cohort introduced limitations into the studies. The inclusion/exclusion criteria limit recruitment to those without dominant upper limb paralysis and who had a baseline mRS≤3. Hence the study samples do not represent a general stroke sample and therefore the studies are not generalizable. The use of the inclusion/exclusion criteria have resulted in a younger population in ESPRIT than most stroke populations.

Another limitation of this study was that we were underpowered to examine the interaction of recurrent vascular event and CIND-moderate status at baseline. However, as we controlled for the recurrence of stroke as well as the history of previous strokes, we believe that our sample size will not affect our conclusions. Whilst pre-stroke dementia was excluded, we were unable to control for pre-stroke cognitive impairment. Furthermore, although the cognitive battery utilized was validated by administration to an elderly community dwelling population in Singapore in order to elicit formal structural domains, identify items that may not be culturally relevant, and to replace those items with culturally appropriate items; more studies need to be performed using other cognitive instruments to confirm the predictive abilities of the CIND-moderate classification.

We recognize that our findings may be due to the definitions of CIND severity and MCI subgroups, which results in CIND-moderate representing more global cognitive impairments than either form of multi-domain MCI, and also results in CIND mild overlapping with multi-domain MCI. As there are four MCI subclassifications compared to the two CIND subclassifications that we proposed, this may result in a loss of power in this study for the MCI subclassification, which could explain our results. Additionally, we recognize that our classifications of CIND did not adopt the typical threshold of less than one standard deviation from the mean, but instead adopted the usual MCI threshold of <1.5 standard deviations from the mean so as to allow comparison.

Study II

In addition to the limitations mentioned above, we did not have information pertaining to the baseline NIHSS score in the study sample, and therefore we were unable to control for neurological impairments amongst this stroke cohort. The inability to control for neurological impairments may confound the association between baseline cognitive status and death, dependency, and recurrent vascular events.

Unlike in Study I, we did not utilize MCI subtypes (amnestic single domain MCI, amnestic multiple domain MCI, non amnestic single domain MCI, non amnestic multiple domain MCI) in our analysis, as the number of outcomes was small. In addition, we chose to examine CIND and not MCI as strokes may produce a spectrum of cognitive changes, but may not necessarily produce prominent amnesia, as is emphasized in the MCI subtypes.

Furthermore, the use of the conservative Bonferroni correction method in all analyses pertaining to domain specific impairments may underestimate the contributions of these domains. In this study, without the use of a correction method, there was an effect of the language domain on vascular events as well as the verbal memory on death. However, we suggest that such findings require further confirmation.

Study III

The outcome of dementia in this study should be considered to be hospitalization for or death due to dementia, as it was derived from population based registers (NPR and CDR). Previous studies have estimated that only about half of all dementia cases are captured in the registers since hospitalization or death due to dementia as the primary cause is relatively uncommon (the specificity and positive predictive value of dementia diagnoses are close to 100%)[71]. In addition, dementia cases that are captured in the NPR are likely to be more severe.

Another limitation is that persons who had an ORD score of 3 in this study fell into the following categories: (a) false positives, meaning that they were visited and worked up

and it was determined that they were not demented; (b) those who refused to be worked up; (c) those who were deliberately not worked up because their twin partner was already dead. This introduces the possibility that some of those with an ORD score of 3 were actually demented, and therefore should have been excluded from the study. However, the presence of a dose response relationship between the ORD score and the risk of dementia, death, or hospitalization suggests that the underlying findings are valid. We also performed additional analyses limiting the cohort analyses to the persons in the within-pair analyses to ensure that the underlying findings are valid and not the result of a smaller sample size. An example of cohort and within pair analyses restricted to the same sample is presented in Table 8.

	Cohort Analyses			MZ only		
	OR	95% CI		OR	95% CI	
ORD 0	1.00	- -		1.00	- -	
ORD 1	**1.55**	**1.33**	**2.07**	1.07	0.53	2.15
ORD 2	**2.67**	**1.22**	**3.67**	0.62	0.22	1.80
ORD 3	**3.54**	**1.99**	**6.78**	1.11	0.37	3.39
no CIND	1.00	- -		1.00	- -	
CIND	**1.71**	**1.21**	**2.52**	1.03	0.45	2.35
no SCI	1.00	- -		1.00	- -	
SCI	**1.72**	**1.11**	**2.67**	**3.17**	**1.22**	**11.67**

Table 8: Cohort and MZ only analyses of the association between cognitive exposures and dementia limited to the same persons

In addition, while the use of the TELE facilitates cognitive testing in large-scale studies such as HARMONY, they do not allow for subtype analyses that may be undertaken if neuropsychological test batteries were used instead. Unfortunately, we only have genetic data for those who underwent clinical workup, and therefore are unable to directly examine the role of genes in this study. Lastly, the cross sectional nature of our cognitive data limits our ability to disentangle the effect of cognitive status from that of cognitive decline in attempting to look at the relationship between cognition and negative health outcomes.

Study IV

In addition to the limitations discussed in Study III, additional limitations exist for the analyses presented in Study IV. Firstly, the cross sectional nature of our cognitive and depression data limits our ability to disentangle the effects of the temporal evolutions

of depression and cognitive impairment in this study. Secondly, the large gap in time between the evaluation of the cognitive and depressive symptoms and the beginning of the PDR may introduce biases in the dataset as persons may have evolved in both depressive and cognitive status. However, as we were able to see strong associations between medication use in both whole cohort and the restricted analyses and therefore do not believe that these results are an artifact. Thirdly, the use of the PDR for ascertainment of medication use poses several problems: while we are able to ascertain who purchased the antidepressant and cardiovascular medication, we are unable to determine whether these medications are actually consumed; the duration of treatment and the dose of medication could also not be determined.

If never depressed

N=8,916	No medications			DEP medications			CVD medications		
	HR	95%	CI	HR	95%	CI	HR	95%	CI
CIND	2.03	1.71	2.41	1.71	1.36	2.15	1.71	1.36	2.15
SCI	1.58	1.33	1.89	1.55	1.24	1.95	1.54	1.25	1.98
Dep med	-	-	-	2.04	1.4	2.98	-	-	-
CVD med	-	-	-	-	-	-	0.56	0.44	0.72

If 1st diagnosis of depression before age 65

N=458	No medications			DEP medications			CVD medications		
	HR	95%	CI	HR	95%	CI	HR	95%	CI
CIND	1.52	0.74	3.11	1.19	0.41	3.45	1.22	0.43	3.47
SCI	1.7	0.84	3.45	1.14	0.47	2.76	1.14	0.47	2.75
Dep med	-	-	-	1.31	0.38	4.55	-	-	-
CVD med	-	-	-	-	-	-	0.73	0.27	1.92

If 1st diagnosis of depression after age 65

N=1.777	No medications			DEP medications			CVD medications		
	HR	95%	CI	HR	95%	CI	HR	95%	CI
CIND	1.29	0.89	1.87	1	0.58	1.73	1	0.58	1.73
SCI	1.56	1.04	2.34	1.69	0.96	2.97	1.72	0.98	3.01
Dep med	-	-	-	2.05	1.07	3.91	-	-	-
CVD med	-	-	-	-	-	-	0.49	0.28	0.86

Table 9: Association between cognitive and pharmaceutical exposures and risk of dementia when controlling for no, antidepressant, or cardiovascular medication use stratified by depression status.

In addition, while the results of this study suggest that antidepressant use is associated with dementia, it is possible that the results are confounded by indication. It is therefore possible that the underlying depression that warranted the antidepressant prescription is associated with dementia rather than the antidepressant itself. In order to disentangle these results, we present results

stratified by depression status in Table 9 that indicates that antidepressant medication use increases the risk of dementia even in persons without depression. However, even with stratified analyses, it is possible that confounding by indication persists.

7 GENERAL DISCUSSION & REFLECTIONS

The manuscripts in this thesis have all examined various aspects of the associations between cognitive impairment and negative health outcomes such as dementia, death, dependency, hospitalization, and vascular events. The overall aim of this thesis was to highlight the fact that persons with cognitive impairment, even in the milder forms (i.e. not dementia), have poorer outcomes than their unimpaired counterparts. As current medical practices do not provide these subjects with a higher level of care, these subjects may represent a neglected group where changes in public health focus may bring benefits.

In Studies I and II we were able to show within stroke patients, patients with CIND have an increased risk of dementia, death, and dependency (Figure 8). Even within patients with CIND, we were able to identify a subset of patients that were particularly at risk for dementia and death. Using cognitive status to identify these persons at high risk will enable healthcare workers and family members to prepare for the patient's eventual care needs. Additionally, it identifies a group of patients most in need of interventions to delay the progression of disease.

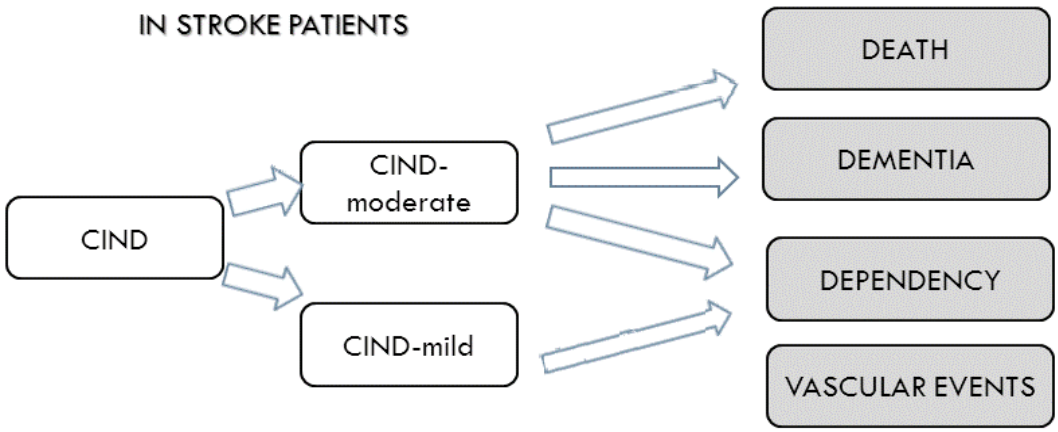

Figure 8: Summarized findings from Studies I and II

In Studies III and IV, we were able to confirm previous reports that persons with CIND are at an increased risk of negative health outcomes. However, we were able to build on these studies by attempting to understand the mechanisms behind this increased risk. We were also able to highlight the role of medication use in the pathogenesis of dementia.

Figures 9a and b summarize the main findings of Studies III and IV. CIND can be interpreted as a marker of underlying disease process that predisposes persons to dementia, death, and hospitalization. On the other hand, SCI appears to be an independent predictor of dementia. Difficulties with medication appear to be one mechanism by which CIND is associated with dementia. However, it is a strong predictor of mortality and pharmaceutical aids that facilitate the proper usage of medications may improve mortality rates among the elderly. Lastly, the finding that persons with SCI and CIND get more antidepressant and less cardiovascular medication highlights the fact that the persons who may need these interventions the most are not getting them.

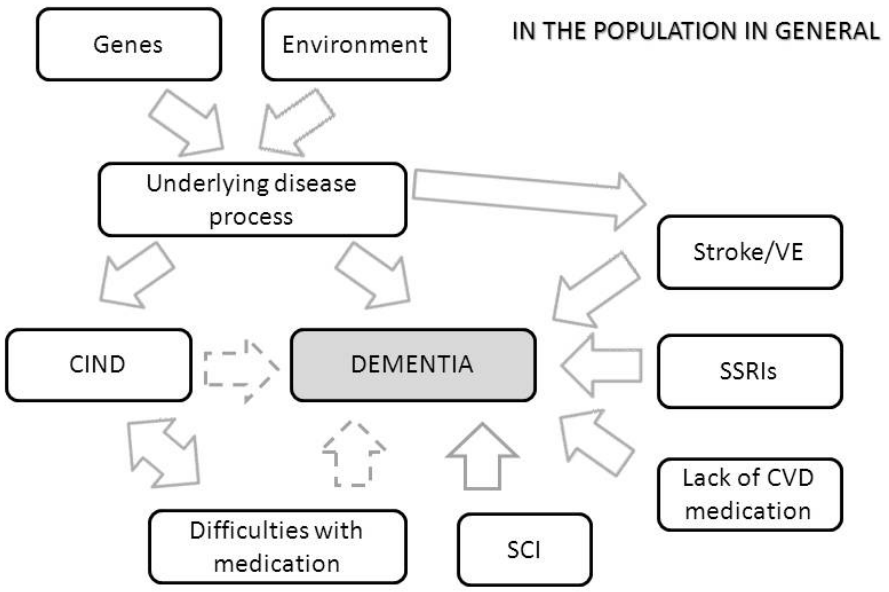

Figure 9a: Summarized findings from Studies III and IV—Dementia

Ultimately, regardless of the mechanisms behind the increased risk of negative health outcomes, one thing is clear: People with cognitive impairment (both in the general population and in high risk subgroups such as stroke patients) should be seen more regularly by their healthcare professionals than currently practiced. Since many of the non-demented persons with cognitive impairment are relatively independent, it is unclear whether they receive more attention from their healthcare providers than persons without cognitive impairments. While it may be argued that the healthcare infrastructures in most countries may not be able to support such close follow up of cognitively impaired persons, I believe that more emphasis needs to be given to

persons with pre-dementia than is currently being given because that is our one opportunity to delay or prevent dementia.

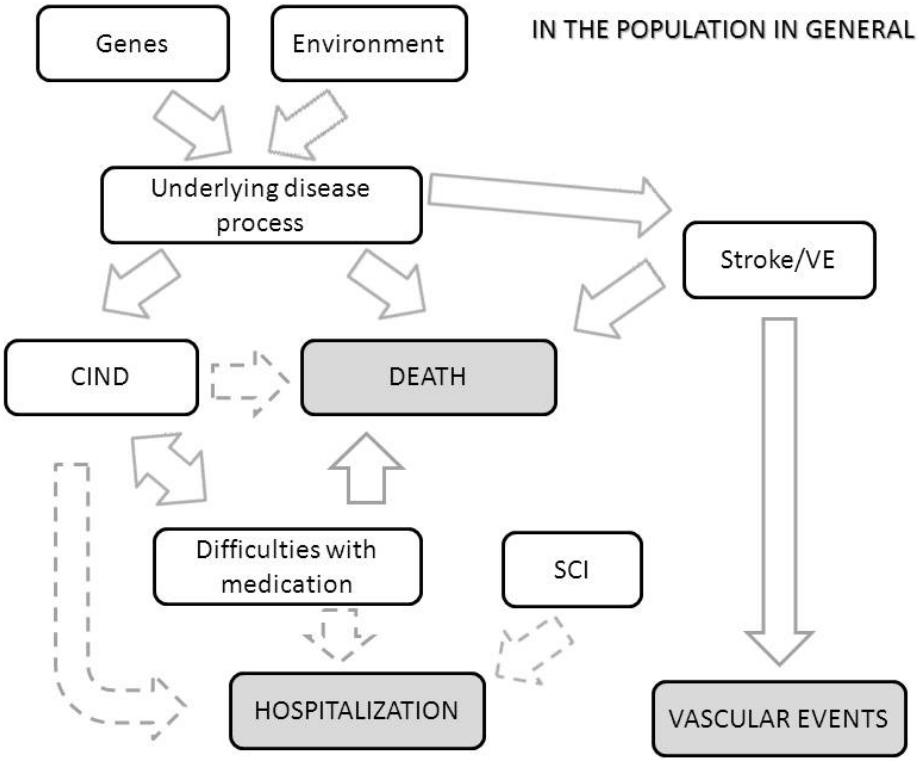

Figure 9b; Summarized findings from Studies III and IV – Death, Hospitalization, and Vascular Events

Personally, I believe that a good analogy for pre-dementia and dementia is the different stages of cancer. I think of persons with pre-dementia as having the equivalent of a stage one or two cancer. Although there is a potential for progression to stage three or four, there is also a chance that you can reverse or arrest the progression of the disease. The focus should be on aggressive interventions so as to delay or prevent the onset of more severe disease (i.e. dementia). Once you've reached the later stages, and have developed dementia, the goal of therapy changes to one of a more supportive nature. However, as with cancer, it may be that early detection and treatment of cognitive impairment may only result in an apparent improvement of outcomes due to complications with lead-time bias. However, it is premature to conclude if this will be the case with cognitive impairment and dementia.

Part of the problem with this analogy is that we currently lack the aggressive therapy that is needed to prevent or delay the onset of dementia. In the last ten years, medical research has focused on reducing mortality. Much of the research (in terms of personnel, publications, and funding) has focused on cancer and heart disease in particular, two diseases that are leading causes of mortality in the developed world. Accordingly, the fields of cardiology and oncology have seen considerable improvement in unraveling the mechanisms behind disease. This has led to improvements in the availability of therapies in the respective fields. (Figure 10) Neurological disorders, however, have not seen the same level of growth in terms of research. Perhaps ten years down the road, with an ever-extending life expectancy, greater interest will be shown in diseases that have high morbidity. One wonders if that will be too little too late.

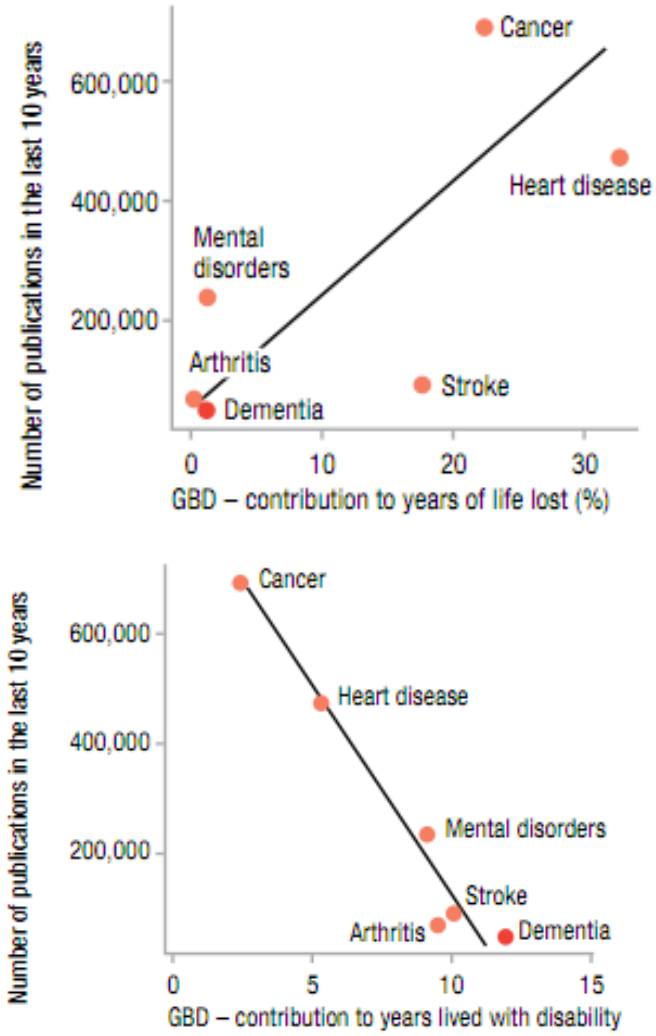

Figure 10: Correlation of research effort (publications from last 10 years) with contributions to mortality and disability for six major chronic diseases. Source: World Alzheimer's Report 2009, Executive Summary

8 CONCLUSIONS

In general, this thesis shows that persons with cognitive impairment have poorer health outcomes than their cognitively normal counterparts. In particular, persons with cognitive impairment are at increased risk of dementia, death, and disability. Persons with cognitive impairment are at additional risk of negative health outcomes due to difficulties with medication and because cognitive impairment acts as a marker of underlying disease. In addition, we were able to show that persons with cognitive impairment get less cardiovascular medications and more antidepressant medications, both of which increase the risk of dementia. The specific conclusions are as follows:

In stroke patients

- CIND predicts dementia, dependency, and death.
- CIND severity discriminates patients who are at high risk of dementia and death
- CIND severity performs as well as MCI subtypes in a stroke population
    - But given the emphasis on memory in MCI and the simplicity of CIND severity, CIND severity may be more relevant in a post stroke setting

In the general population

- CIND predicts dementia and death and time to hospitalization
    - This association is explained mostly by genetic and shared environmental factors
- SCI predicts dementia and time to hospitalization independent of genetic and shared environmental factors
- Difficulties with medication predict mortality and dementia and may be a modifiable risk factor.
- Selective Serotonin Reuptake Inhibitors (SSRIs) double the risk of dementia
    - Persons with CIND and SCI receive more of these medications than their unimpaired counterparts
- Antihypertensives and lipid-lowering agents are protective for dementia
    - Persons with CIND and SCI receive less of these medications than their unimpaired counterparts

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I

Severity of CIND and MCI predict incidence of dementia in an ischemic stroke cohort

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ABSTRACT

Background: The utility of poststroke cognitive status, namely dementia, cognitive impairment no dementia (CIND), mild cognitive impairment (MCI), and no cognitive impairment (NCI), in predicting dementia has been previously examined. However, no studies to date have compared the ability of subtypes of MCI and CIND to predict dementia in a poststroke population.

Methods: A cohort of ischemic stroke patients underwent neuropsychological assessment annually for up to 5 years. Dementia was defined using the *DSM-IV* criteria. Univariate and multivariable Cox proportional regression was performed to determine the ability of MCI subtypes, CIND severity, and individual domains of impairment to predict dementia.

Results: A total of 362 patients without dementia were followed up for a mean of 3.4 years (17% drop out), with 24 developing incident dementia. Older age, previous and recurrent stroke, and CIND and MCI subtypes were significant predictors of dementia. In multivariable analysis controlling for treatment allocation, patients who were older, had previous or recurrent stroke, and had either CIND moderate or multiple domain MCI with amnestic component were at elevated risk for dementia. In multivariable domain analysis, recurrent strokes, age, and previous strokes, verbal memory, and visual memory were significant predictors of dementia. Receiver operating characteristic curve analysis showed that CIND moderate (area under the curve: 0.893) and multiple domain MCI with amnestic component (area under the curve: 0.832) were significant predictors of conversion to dementia. All other classifications of cognitive impairment had areas under the curve less than 0.7.

Conclusion: Stroke patients with cognitive impairment no dementia (CIND) moderate are at higher risk of developing dementia, while CIND mild patients are not at increased risk of developing dementia. ***Neurology*® 2009;73:1866–1872**

GLOSSARY

AD = Alzheimer disease; **AUC** = area under the curve; **CI** = confidence interval; **CIND** = cognitive impairment no dementia; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition; **ESPRIT** = European Australasian Stroke Prevention in Reversible Ischemia Trial; **ESPRIT-Cog** = European Australasian Stroke Prevention in Reversible Ischemia Trial, cognitive substudy; **HR** = hazard ratio; **LACI** = lacunar infarct; **MCI** = mild cognitive impairment; **mRS** = modified Rankin scale; **NCI** = no cognitive impairment; **OCSP** = Oxfordshire Community Stroke Project; **PACI** = partial anterior circulation infarct; **POCI** = posterior circulation infarct; **ROC** = receiver operating curve; **TACI** = total anterior circulation infarct; **VaD** = vascular dementia; **WAIS-R** = Wechsler Adult Intelligence Scale–Revised; **WMS-R** = Wechsler Memory Scale–Revised.

Dementia, mild cognitive impairment (MCI), and cognitive impairment no dementia (CIND) are frequently underdiagnosed and their incidence is likely to increase in aging populations. CIND and MCI are concepts that are commonly used to define the transitional period between normal aging and dementia. CIND has a broad scope, and is used to define impairments in any objective cognitive domains in neuropsychological testing in the absence of dementia.[1] MCI was originally identified as a precursor to Alzheimer disease (AD) and defined as a complaint of defective memory with an abnormal memory function for age, along with normal activities of daily living, normal general cognitive functioning, and absence of dementia.[2] More recently, MCI definitions have been categorized into 4 subtypes: amnestic MCI, nonamnestic

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single domain MCI, multiple-domain MCI with amnestic component, and nonamnestic multiple domain MCI.[3]

While comparisons of the predictive ability of MCI and CIND have been conducted in epidemiologic settings,[4] they have not been performed in poststroke patients, who are known to have a high risk of dementia.[5] The broad definition of CIND has been shown to be unstable in a poststroke setting.[6] We therefore aimed to determine which CIND subtype predicts for dementia among poststroke patients. We also aimed to compare CIND and MCI subtypes as predictors of dementia and assessed the ability of cognitive domains to predict dementia.

METHODS

Subjects. All patients with recent TIAs or nondisabling ischemic stroke who were seen in the Singapore General Hospital between 1999 and 2005 were screened for eligibility for the European Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT). Detailed methodology for the main study have been previously reported.[7] Briefly, patients were eligible if they were within 6 months of a TIA (including transient monocular blindness) or nondisabling ischemic stroke (grade ≤3 on the modified Rankin scale[8]) (mRS) of presumed arterial origin. The exclusion criteria were a possible cardiac source of embolism, high-grade carotid stenosis for which carotid endarterectomy or endovascular treatment was planned, any blood coagulation disorder, any contraindication for aspirin or dipyridamole, and a limited life expectancy.

Patients recruited into ESPRIT were eligible to enter this cognitive substudy (ESPRIT-Cog) with the following additional exclusion criteria: confusion, severe aphasia (expressive or receptive), major psychoses diagnosed according to *DSM-IV* criteria,[9] or dominant upper limb paralysis.

Standard protocol approvals, registrations, and patient consents. The study protocol was approved by Singapore General Hospital's Institutional Review Board and Ethics Committee. Written informed consent was obtained from all patients or legal guardians. The ESPRIT Trial was registered under clinicaltrials.gov with the identifier NCT00161070.

Neuropsychological test battery. Patients who consented to ESPRIT-cog received their baseline cognitive assessment 3 to 4 months after their qualifying event and annually thereafter for up to 5 years. Trained research psychologists administered a neuropsychological test battery that has previously been validated for use in Singapore.[10] The battery assessed 6 domains, 4 of which were nonmemory domains. Education-adjusted cutoffs of 1.5 standard deviations below established normal means were used on individual tests. Failure in at least half of the tests in a domain constituted failure in that domain. The assessment was administered in English, Malay, Mandarin, or Chinese dialects according to the subject's habitual language. The entire battery took under an hour and a half to complete.

The nonmemory domains were Attention, as defined by Digit Span,[11] Visual Span,[11] and Auditory Detection; Language, as defined by Modified Boston Naming and Category Fluency (Animals and Food subtasks); Visuomotor speed, as defined by Symbol Digit Modality Test,[12] Digit Cancellation,[13] and Maze Task[14]; and Visuoconstruction, as defined by Wechsler Memory Scale–Revised (WMS-R)[11] subtest Visual Reproduction Copy task, Clock Drawing, and Wechsler Adult Intelligence Scale–Revised (WAIS-R)[15] Block Design subtest.

The memory domains were Verbal Memory, as defined by Word List Recall[16] (Immediate, Delayed, and Delayed Recognition) and Story Recall (Immediate and Delayed); and Visual Memory, as defined by Picture Recall (Immediate, Delayed, and Delayed Recognition) and WMS-R Visual Reproduction[11] (Immediate, Delayed, and Delayed Recognition).

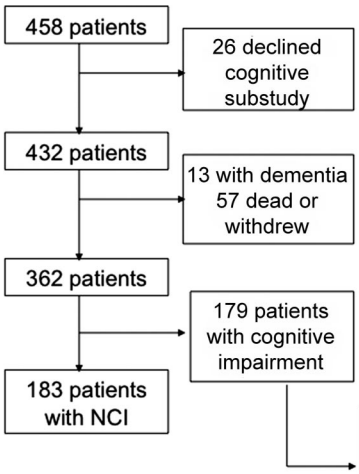
Diagnosis of dementia. Diagnoses of dementia were made at weekly consensus conferences that were attended by neurologists, neuropsychologists, research nurses, and research assistants. Diagnoses were made according to the *DSM-IV*[9] criteria. CT, MRI, and magnetic resonance angiography were reviewed as part of the diagnostic process. The etiologic diagnoses followed the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for AD[17] and the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche en l'Enseignement en Neurosciences criteria[18] for vascular dementia (VaD). The sample without dementia included individuals with diagnoses of CIND, MCI, or no cognitive impairment (NCI). Patients with CIND were impaired in at least one domain of the neuropsychological test battery, but did not meet criteria for dementia.[1] On the basis of the sample median, CIND was divided into CIND mild (1–2 domains impaired) and CIND moderate (3–6 domains impaired). Patients were also classified by MCI subtypes (amnestic MCI, nonamnestic single domain MCI, multiple domain MCI with an amnestic component, and nonamnestic multiple domain MCI) according to the revised MCI criteria.[3]

Baseline risk factors. Risk factor information was collected at baseline. Stroke subtype was classified according to the Oxfordshire Community Stroke Project (OCSP)[19] as total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), posterior circulation infarct (POCI), or lacunar infarct (LACI).[19] Vascular risk factor data, such as age, diabetes mellitus status, hypertension, hyperlipidemia, smoking status, ischemic heart disease, peripheral artery disease, as well as past history of stroke, angina, and myocardial infarction were obtained verbally from the patient and confirmed with hospital records.

Outcome measures. Patients were followed up annually for up to 5 years. Patients underwent full neuropsychological assessment at the outpatient clinic. If a recurrent event had occurred, detailed hospital records were obtained to verify the occurrence of the vascular event.

Statistical analysis. Analysis of variance or χ^2 analysis was used to test for significant differences among NCI, CIND mild, and CIND moderate patients. Analysis was done in 3 stages. In the first stage, univariate regressions were performed to determine which baseline characteristics were predictive of dementia. Univariate regression analyses were repeated 3 times, once with CIND severity as the indicator of baseline cognitive impairment, then with an indicator of 1 domain of impairment vs multiple domains of impairment, and again with MCI subtypes as the indicator of cognitive impairment. In the second stage of analyses, multivariable regression models controlling for treatment allocation were performed with significant predictors in the univariate stage being included in the models. Analyses were re-

Figure Study design



	CIND mild	CIND moderate
Amnestic MCI (SD)	20	0
Nonamnestic MCI (SD)	33	0
Amnestic MCI (MD)	21	78
Nonamnestic MCI (MD)	20	7

peated again with CIND severity and MCI subtypes as indicators of baseline cognitive impairment. In the third stage of analysis, individual domains of cognition were analyzed for their ability to predict conversion to dementia in both univariate analyses, and multivariable analyses which adjusted for significant predictors of dementia from stage 1, and treatment allocation. Cox proportional hazards models were used in all stages of analyses. Analyses were performed in Stata 10.0,[20] and significance was determined with a 2-tailed alpha of 0.05 in stages 1 and 2 of analyses while Bonferroni adjustment for multiple comparisons in stage 3 yielded an alpha of 0.008. Finally, uniform scores were derived for each domain and averaged across the patients in different MCI and CIND severity, after which receiver operating curves (ROC) were plotted to compare the area under the curve (AUC) of the different classifications.

RESULTS A total of 458 patients were recruited into ESPRIT at the Singapore General Hospital site, of which 432 consented to participate in the ESPRIT-cog substudy (figure). Of these 432 patients, 13 had dementia at baseline, and 57 died or withdrew from the study before undergoing follow-up neuropsychological evaluation. We thus present data of 362 patients (mean age 60 ± 11 years, 30% women) who were followed for an average of 3.2 years. There were 183 patients with NCI, 94 with CIND mild, and 85 with CIND moderate. The demographic characteristics of the study population stratified by baseline cognitive status are summarized in table 1. Patients with more severe cogni-

Table 1 Demographic characteristics of the patient population

	NCI (n = 183), n (%)	CIND mild (n = 94), n (%)	CIND moderate (n = 85), n (%)	Amnestic MCI (S) (n = 20), n (%)	Nonamnestic MCI (S) (n = 33), n (%)	Amnestic MCI (M) (n = 99), n (%)	Nonamnestic MCI (M) (n = 27), n (%)	*p* Value*	*p* Value†
Age, y, mean (SD)	55 (10)	64 (10)	66 (10)	59 (9)	65 (10)	66 (10)	65 (10)	<0.0001‡	<0.001‡
Women	40 (22)	36 (38)	34 (40)	3 (15)	11 (33)	38 (38)	18 (67)	0.002‡	<0.001‡
Diabetes mellitus	57 (31)	43 (46)	44 (52)	7 (35)	15 (45)	49 (49)	16 (59)	0.002‡	0.006‡
Hypertension	122 (67)	76 (81)	67 (79)	18 (90)	26 (79)	77 (78)	22 (81)	0.017‡	0.052
Previous stroke	24 (13)	20 (21)	17 (20)	4 (20)	7 (21)	20 (20)	6 (22)	0.154	0.439
Hyperlipidemia	80 (44)	43 (46)	37 (44)	9 (45)	14 (42)	42 (42)	15 (56)	0.940	0.808
Ever smoker	70 (38)	35 (37)	26 (31)	13 (65)	11 (33)	32 (32)	5 (18)	0.464	0.018‡
Previous ischemic heart disease	17 (9)	10 (11)	11 (13)	3 (15)	4 (12)	11 (11)	3 (11)	0.662	0.93
Previous peripheral artery disease	4 (2)	2 (2)	3 (4)	0 (0)	1 (3)	4 (4)	0 (0)	0.779	0.682
Previous angina pectoris	16 (9)	7 (7)	6 (7)	3 (15)	3 (6)	6 (6)	2 (7)	0.870	0.708
Previous myocardial infarction	5 (3)	3 (3)	4 (5)	1 (5)	2 (6)	4 (4)	0 (0)	0.701	0.693
Modified Rankin Scale score, median (IQR)	0 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	0.0001‡	0.0001‡
Stroke subtype									
TIA	52 (28)	15 (16)	3 (4)	2 (10)	3 (9)	9 (9)	4 (15)	<0.0001‡	0.002‡
POCI/LACI	121 (66)	69 (73)	71 (84)	16 (80)	24 (72)	80 (80)	20 (74)		
TACI/PACI	10 (6)	10 (11)	11 (13)	2 (10)	6 (18)	10 (10)	3 (11)		

*p Value of comparisons among NCI, CIND mild, and CIND moderate.
†p Value of comparisons between NCI and MCI subtypes.
‡Significant.
NCI = no cognitive impairment; CIND = cognitive impairment no dementia; MCI = mild cognitive impairment; S = single domain; M = multiple domain; IQR = interquartile range; POCI = posterior circulation infarct; LACI = lacunar infarct; TACI = total anterior circulation infarct; PACI = partial anterior circulation infarct.

Table 2 Results of univariate and multivariable Cox proportional hazards models for the prediction of dementia (condensed version)

	Univariate		Multivariate*	
	HR	95% CI	HR	95% CI
Baseline cognitive status				
NCI†	1.00	—	1.00	—
CIND mild	4.39	0.80–24.0	1.04	0.17–6.37
CIND moderate	22.5	5.22–97.2‡	6.43‡	1.30–31.7‡
NCI†	1.00	—	1.00	—
Single domain impairment	3.83	0.53–27.2	1.07	0.14–8.24
Multiple domain impairment	16.9	3.94–72.3‡	4.72	0.97–22.94
NCI†	1.00	—	1.00	—
Amnestic MCI	4.92	0.45–54.3	2.26	0.18–27.7
Nonamnestic single domain MCI	3.13	0.28–34.5	0.62	0.05–7.58
Multiple domain MCI with amnestic component	19.3	4.48–83.4‡	5.77	1.19–28.0‡
Nonamnestic multiple domain MCI	7.87	1.11–55.9‡	1.06	0.12–9.21
Stroke subtype				
TIA†	1.00			
POCI/LACI	6.48	0.87–48.2		
TACI/PACI	4.85	0.44–53.5		
Age	1.12	1.07–1.17‡	1.08	1.03–1.14‡
Baseline modified Rankin Scale score	2.50	1.75–3.55‡	1.91	1.21–3.01‡
Baseline MMSE score	0.91	0.83–0.99‡	1.00	0.88–1.15
Previous stroke	2.70	1.18–6.19‡	3.01	1.81–7.67‡
Recurrent stroke	5.57	2.49–12.4‡	2.45	1.02–5.92‡

*Controlled for treatment allocation.
†Reference group.
‡Significant.
HR = hazard ratio; CI = confidence interval; NCI = no cognitive impairment; CIND = cognitive impairment no dementia; MCI = mild cognitive impairment; POCI = posterior circulation infarct; LACI = lacunar infarct; TACI = total anterior circulation infarct; PACI = partial anterior circulation infarct; MMSE = Mini-Mental State Examination.

tive impairment were significantly older; more likely to be women, diabetic, and hypertensive; and more likely to have had more severe stroke.

Among the 179 patients with MCI, 20 had amnestic MCI, 33 nonamnestic single domain MCI, 99 multiple-domain MCI with amnestic component, and 27 nonamnestic multiple domain MCI.

During the course of the study, 24 patients converted to dementia: 3 AD, 15 VaD, and 6 mixed dementia. The incidence of dementia was 11 per 1,000 in NCI patients, 42 per 1,000 in CIND mild patients, and 212 per thousand in CIND moderate patients. By MCI subtypes, the incidence of dementia for MCI subtypes was 11 in NCI, 50 in amnestic MCI, 30 in nonamnestic single-domain MCI, 181 in multiple-domain MCI with amnestic component, and 74 in nonamnestic multiple domain MCI patients.

In univariate analysis, older patients, patients with prior strokes, patients who experienced another stroke, as well as those with more severe baseline cognitive impairment (CIND moderate, hazard ratio [HR] = 22.5, confidence interval [CI] 5.22–97.2, in CIND severity; multiple domain MCI with amnestic component, HR = 19.3, CI 4.48–83.4; and nonamnestic multiple domain MCI, HR = 7.87, CI 1.11–55.9, in MCI subtypes, and MMSE, HR = 0.91, CI 0.83–0.99) were at higher risk of conversion to dementia (table 2 [condensed version], table e-1 on the *Neurology*® Web site at www.neurology.org [full version]).

In multivariable analysis controlling for treatment allocation, age (HR = 1.08, CI 1.03–1.14), occurrence of a previous stroke (HR = 3.01, CI 1.18–7.67), occurrence of another stroke (HR = 2.45, CI 1.02–5.92), and baseline cognitive status as defined by either CIND moderate (HR = 6.43, CI 1.30–31.7) or multiple domain MCI with amnestic component (HR = 5.77, CI 1.19–28.0) were significant predictors of dementia (table 2 [condensed version], table e-1 [full version]).

Table 3 summarizes impairment of cognitive domains stratified by the number of domains impaired. Visuomotor speed was the domain that was most commonly impaired, followed by visuoconstruction and visual memory. In univariate domain analysis, all domains were significant predictors of dementia (table 3). In multivariable domain analysis, while verbal memory, visual memory, visuoconstruction, and visuomotor speed were significant at an alpha of 0.05, only verbal memory (HR = 6.92, $p < 0.001$) and visual memory (HR = 4.25, $p = 0.002$) were significant predictors of dementia after Bonferroni adjustment (table 3).

ROC curve analysis showed that CIND moderate (AUC 0.893) was not significantly better than multiple domain MCI with amnestic component in predicting dementia (AUC 0.832) ($p = 0.50$). All other classifications of cognitive impairment had AUCs less than 0.7.

DISCUSSION In this study, we evaluated the ability of CIND severity to predict dementia in a poststroke population. The CIND severity (CIND mild and CIND moderate) were able to differentiate patients who were at risk of conversion to dementia. CIND moderate patients had a sixfold increased risk of conversion to dementia compared to NCI patients while CIND mild patients' risk was similar to that of NCI patients. Both multidomain MCI subtypes and CIND moderate subtypes were able to predict incident dementia. We confirmed findings from prior studies which showed that age, the occurrence of a prior stroke, and

Table 3 Distribution of domains of impairment and results of univariate and multivariable Cox proportional hazards models with domains of impairment as the exposure

	No.	Attention	Language	Verbal memory	Visual memory	Visuoconstruction	Visuomotor speed
No. (%) impaired							
TIA patients	70	1 (2)	0 (0)	5 (8)	9 (13)	10 (14)	11 (15)
LACI/POCI patients	261	21 (8)	23 (8)	39 (17)	85 (33)	92 (35)	104 (41)
TACI/PACT patients	31	7 (22)	5 (16)	4 (17)	11 (35)	13 (43)	16 (55)
In patients with							
1 domain impaired	53	0 (0)	1 (2)	3 (6)	17 (32)	10 (19)	20 (38)
2 domains impaired	41	2 (4)	3 (6)	7 (13)	16 (30)	26 (49)	29 (55)
3 domains impaired	43	6 (14)	2 (5)	10 (23)	32 (74)	38 (88)	40 (93)
4 domains impaired	24	8 (33)	7 (29)	12 (50)	22 (92)	23 (96)	24 (100)
5 domains impaired	12	7 (58)	7 (58)	10 (83)	12 (100)	12 (100)	12 (100)
6 domains impaired	6	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)
Total	179	29 (16)	26 (15)	48 (27)	105 (59)	115 (64)	131 (73)
Regression analysis							
Univariate HR		4.96*	5.01*	8.74*	6.45*	6.10*	13.7*
p Value		<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
Multivariable HR†		1.81	3.07	6.92*	4.25*	3.34	4.37
p Value		0.223	0.015	<0.001*	0.002*	0.014	0.025

All cells reported as n (%) unless otherwise specified.
*Significant.
†Multivariable models adjusted for age, previous stroke, recurrent stroke, baseline modified Rankin Scale, and treatment allocation. Frequency of impairment in each cognitive domain stratified by total number of domains impaired.
LACI = lacunar infarct; POCI = posterior circulation infarct; TACI = total anterior circulation infarct; PACI = partial anterior circulation infarct; HR = hazard ratio.

the occurrence of recurrent strokes were all significant predictors of dementia. We also found that impairments in the domains of verbal and visual memory were able to predict incident dementia.

While prestroke cognitive decline is associated with poststroke dementia,[21] there have been only a few studies examining cognitive states after stroke and their association with incident dementia. One study[22] assessed poststroke survivors without dementia at 3 and 15 months but found that none of the criteria utilized at baseline (MCI, age-associated cognitive decline, vascular CIND) identified patients at risk of incident dementia. Another study[23] examined the predictive accuracy of MCI subtypes for dementia in a mixed cohort of memory clinic and poststroke patients, and showed that the multiple domain MCI subtype had a high sensitivity but did not investigate CIND severity. Finally, a more recent study[24] determined the frequency of CIND in a poststroke population and found that it predicted for incident dementia. However, there was no attempt to differentiate between mild and moderate CIND.

Previous studies comparing patients with incident AD and patients with VaD have shown few differences in their preclinical cognitive profiles.[25-28] However, the lack of difference could well be an artifact of the requirement of memory impairment for a diagnosis of dementia in the *DSM-IV* criteria. An early analysis of subjects with vascular CIND in the Canadian Study of Healthy Aging found that impairments in tests of memory and category fluency were associated with incidence of dementia.[29] However, a later analysis of subjects with NCI from the same study,[30] which investigated neuropsychological predictors, found that while abstract reasoning scores were lower in the incident vascular cognitive impairment group, memory test scores were lower in the incident AD group. Therefore, we suggest that in populations with cognitive impairment of predominantly vascular causes, CIND severity be used as opposed to MCI subtypes, which emphasize an amnestic component. Larger epidemiologic studies in populations at risk for cognitive impairment of predominantly vascular causes are needed to confirm our findings. Additionally, our proposed CIND subtype definitions may be supplemented with executive functioning and abstract reasoning tests.

In support of our findings that impairments in the domains of visual memory and verbal memory were associated with an increased risk of incident dementia, the Sydney Stroke Cohort has shown that verbal memory was more likely to deteriorate in isch-

emic stroke or TIA patients who converted to dementia.[31] Cognitive impairment in stroke patients may lead to an increase of mortality and recurrent cerebrovascular events due to several causes. Cognitively impaired patients may be less compliant with medication, thereby reducing the effectiveness of secondary prevention therapies, or be less able to alter their lifestyle habits, which may lead to poorer control of vascular comorbidities.[21] This is particularly important in stroke patients, who tend to have more vascular comorbidities than patients with AD.[32] Therefore, while the initial magnitude of cognitive decline seen among poststroke patients is less than that of patients with prodromal AD,[33] the subsequent effect on mortality and morbidity might be greater than in patients with AD.

Our study has several limitations. The inclusion/exclusion criteria limit recruitment to those without dominant upper limb paralysis and who had a baseline mRS $\leq$3. Hence this may limit the generalizability of our findings as these criteria have resulted in a younger population in ESPRIT than most stroke populations. With only 24 patients progressing to dementia, we were unable to perform separate analysis on patients who progressed to AD, VaD, or mixed dementia. Larger studies should endeavor to investigate the predictive ability of CIND mild and CIND moderate separately in patients who progress to AD and VaD. Another limitation of this study was that we were underpowered to examine the interaction of recurrent vascular event and CIND moderate status at baseline. However, as we controlled for the recurrence of stroke as well as the history of previous strokes, we believe that our sample size will not affect our conclusions. While prestroke dementia was excluded, we were unable to control for prestroke cognitive impairment. Furthermore, although the cognitive battery utilized was validated by administration to an elderly community-dwelling population in Singapore in order to elicit formal structural domains, identify items that may not be culturally relevant, and to replace those items with culturally appropriate items, more studies need to be performed using other cognitive instruments to confirm the predictive abilities of the CIND moderate classification. We recognize that our findings may be due to the definitions of CIND severity and MCI subgroups, which results in CIND moderate representing more global cognitive impairments than either form of multidomain MCI, and also results in CIND mild overlapping with multidomain MCI. As there are 4 MCI subclassifications compared to the two CIND subclassifications that we proposed, this may result in a loss of power in this study for the MCI subclassification, which could explain our results. Additionally, we recognize that our classifications of CIND did not adopt the typical threshold of less than 1 SD from the mean, but instead adopted the usual MCI threshold of $<$1.5 standard deviations from the mean so as to allow comparison. Hence, further studies are needed to validate the operationalized criteria for MCI and CIND in different populations that are at high risk of developing dementia.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Kaavya Narasimhalu.

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DISCLOSURE

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II

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The Prognostic Effects of Poststroke Cognitive Impairment No Dementia and Domain-Specific Cognitive Impairments in Nondisabled Ischemic Stroke Patients

Kaavya Narasimhalu, Sandy Ang, Deidre Anne De Silva, Meng-Cheong Wong, Hui-Meng Chang, Kee-Seng Chia, Alexander P. Auchus and Christopher P. Chen

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The Prognostic Effects of Poststroke Cognitive Impairment No Dementia and Domain-Specific Cognitive Impairments in Nondisabled Ischemic Stroke Patients

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Background and Purpose—There is some evidence that poststroke dementia, cognitive impairment no dementia (CIND), and mild cognitive impairment predict for poor outcomes such as dementia, death, and institutionalization. However, few studies have examined the prognostic value of CIND, CIND severity, and domain impairments in a poststroke cohort.

Methods—A cohort of ischemic stroke patients with baseline cognitive assessments 3 months poststroke were followed up annually for outcomes of dependency, vascular events, and death for up to 5 years. Univariate and multivariate Cox proportional regression was performed to determine the ability CIND, CIND severity, and domain impairments to predict dependency, vascular outcomes, and death.

Results—Four-hundred nineteen patients without dementia (mean age 60±11 years, 32% female) were followed for a mean of 3.2 years. Older age, diabetes, more severe strokes, CIND-mild, and CIND-moderate were independently predictive of dependency. There were no independent predictors of recurrent vascular events. Older age, diabetes, and CIND-moderate were independently predictive of death. In analyses of individual cognitive domains, impairments in visuomotor speed were independently predictive of dependency.

Conclusions—In poststroke patients, CIND predicts dependency and death, while CIND severity discriminates patients with poor survival. Impairments in visuomotor speed independently predict dependency.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique Identifier: NCT00161070.

(*Stroke*. 2011;42:883-888.)

Key Words: dementia ■ stroke ■ mild cognitive impairment ■ cognitive impairment no dementia

Dementia, cognitive impairment no dementia (CIND), and mild cognitive impairment (MCI) have become increasingly prevalent in aging populations. CIND is a broad concept that has been used to define impairments in any objective cognitive domain in neuropsychological testing in the absence of dementia.[1] In community-based studies, CIND has been shown to predict for dementia, death, and institutionalization.[2] One study found that poststroke CIND is a negative predictor of survival.[3] Studies have also shown that poststroke dementia (PSD) increases the risk of recurrent vascular events.[4,5] However, no studies to date have examined the effect of CIND on poststroke recurrent vascular events or dependency. We hypothesize that CIND is associated with dependency, recurrent vascular events, and death following ischemic stroke.

In a previous study from this cohort,[6] we have shown that CIND severity predicts incident dementia; CIND-mild patients shared a similar risk profile with patients with no cognitive impairment (NCI), and CIND-moderate patients experienced a 6-fold increase in the risk of incident dementia. Because PSD has been associated with recurrent vascular events[4] and death,[7] we hypothesize that a similar association may exist with CIND severity and outcomes after stroke.

Previous studies that have examined the prognostic abilities of domain-specific impairments have found that visual memory impairments predict for disturbances in activities of daily living,[8] whereas executive functioning and visuospatial impairments[3,9] predict for poor survival after stroke. Therefore, in this study, we aimed to determine domain-specific

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predictors of dependency, recurrent vascular events, and death.

Methods

Subjects

All patients with recent transient ischemic attacks or nondisabling ischemic stroke who were seen in the Singapore General Hospital between 1999 and 2005 were screened for eligibility for the European Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT). Detailed methodology for the main study has been previously reported.[10] Briefly, patients were eligible if they were within 6 months of a transient ischemic attack (including transient monocular blindness) or a nondisabling ischemic stroke (grade ≤3 on the modified Rankin scale[11] [mRS]) of presumed arterial origin. The exclusion criteria were: a possible cardiac source of embolism, high-grade carotid stenosis for which carotid endarterectomy or endovascular treatment was planned, moderate to severe leukoaraiosis on brain imaging (for randomization into anticoagulation), any blood coagulation disorder, any contraindication for aspirin or dipyridamole, and a limited life expectancy.

Patients recruited into ESPRIT were eligible to enter a cognitive substudy (ESPRIT-Cog) with the following additional exclusion criteria: confusion, severe aphasia (expressive or receptive), major psychosis diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria,[12] or dominant upper-limb paralysis.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was approved by Singapore General Hospital's Institutional Review Board and Ethics Committee. Written informed consent was obtained from all patients or legal guardians. The ESPRIT trial was registered under http://clinicaltrials.gov with the identifier NCT00161070.

Neuropsychological Test Battery

Patients who consented to ESPRIT-Cog received their baseline cognitive assessment 3 to 4 months after their qualifying event, and then annually thereafter for up to 5 years. Trained research psychologists administered a neuropsychological test battery that has been validated for use in Singapore.[13] The battery assessed 6 domains, 4 of which were nonmemory domains. Education-adjusted cutoffs of 1.5 standard deviations below established normal means were used on individual tests. Failure in at least half of the tests in a domain constituted failure in that domain. The assessment was administered in English, Malay, Mandarin, or Chinese dialects according to the subject's habitual language. The entire battery took under 90 minutes to complete.

The nonmemory domains were: Attention, as defined by digit span,[14] visual span,[14] and auditory detection[15]; Language, as defined by modified Boston naming[16] and category fluency[17] (animals and food subtasks); Visuomotor speed, as defined by symbol digit modality test,[18] digit cancellation,[19] and maze ask[20]; and Visuoconstruction, as defined by Weschler Memory Scale–Revised[14] visual reproduction copy task, clock drawing,[21] and Weschler Adult Intelligence Scale–Revised[22] subtest of block design.

The memory domains were: Verbal Memory, as defined by word list recall[23] (immediate, delayed, and delayed recognition) and story recall[14] (immediate and delayed); and Visual Memory, as defined by picture recall[14] (immediate, delayed, and delayed recognition) and Weschler Memory Scale–Revised visual eproduction[14] (immediate, delayed, and delayed recognition).

Determination of CIND

As is commonly defined, patients with CIND were impaired in at least 1 domain of the neuropsychological test battery, but did not meet criteria for dementia.[1] In keeping with our previous study, where severity of CIND predicted incident dementia,[6] CIND was divided by a median split into CIND-mild (1 to 2 domains impaired) and CIND-moderate (3 to 6 domains impaired).

Baseline Risk Factors

Risk factor information was collected at baseline. Stroke subtype was classified according to the Oxfordshire Community Stroke Project[24] by: total anterior circulation infarct, partial anterior circulation infarct, posterior circulation infarct, or lacunar infarct. All patients had either computed tomography or magnetic resonance imaging as part of the diagnostic process. Vascular risk factor data, such as age, diabetes mellitus status, hypertension, hyperlipidemia, smoking status, ischemic heart disease, peripheral artery disease, as well as history of stroke, angina, and myocardial infarction, were obtained verbally from the patient and were confirmed with hospital records.

Outcome Measures

Patients were followed up annually for up to 5 years. Patients underwent full neuropsychological assessment at the outpatient clinic. If a recurrent vascular event had occurred, detailed hospital records were obtained to verify occurrence of the vascular event. Strokes, peripheral artery disease, intracranial bleeds, and any cardiac ischemia (stable and unstable angina, myocardial infarctions) or deaths from any of the above were considered to be a recurrent vascular event. Dependency was measured by the mRS,[11] which is a commonly utilized scale in stroke studies (0=no symptoms, 1=symptoms, no disability, 2=slight disability, 3=moderate disability, 4=moderately severe disability, 5=severe disability, 6=death). The mRS was dichotomized by good outcome (0–2) and bad outcome (3–6). Patients with a mRS of 3 at baseline were considered dependent only if they progressed to mRS scores >3. Information pertaining to death was collected verbally and confirmed with hospital and/or death registry records at the end of the study.

Statistical Analysis

ANOVA or χ^2 analysis was used to test for significant differences between NCI, CIND-mild, and CIND-moderate patients. Analysis was performed in 3 stages. In the first stage, univariate regressions were performed to determine which baseline characteristics were predictive of dependency, recurrent vascular events, and death. Univariate regression analyses were repeated twice, once with CIND versus NCI as the indicator of baseline cognitive impairment, then with CIND severity as the indicator of baseline cognitive impairment. In the second stage of analysis, the analyses were repeated as multivariate regression models controlling for treatment allocation, with significant predictors in the univariate stage included in the models. In the third stage of analysis, individual domains of cognition were analyzed for their ability to predict dependency, recurrent vascular events, or death in both univariate analyses and multivariate analyses (in which domains of cognition were entered individually into regression models that adjusted for significant predictors of dementia from stage 1), and treatment allocation. For the outcome of dependency, we adjusted for stroke subtype, age, gender, diabetes mellitus, hypertension, and treatment allocation. For the outcome of vascular events, we adjusted for age, diabetes mellitus, and treatment allocation. For the outcome of death, we adjusted for age, gender, diabetes mellitus, hypertension, previous myocardial infarction, and treatment allocation. Cox proportional hazards models were used in all stages of analysis. Analyses were performed in Stata 10.0,[25] and significance was determined with a 2-tailed α of 0.05 in stages 1 and 2 of analysis, whereas Bonferroni adjustment for multiple comparisons in stage 3 yielded an α of 0.008.

Results

A total of 458 patients were recruited into ESPRIT at the Singapore General Hospital site, of which 432 consented to participate in the ESPRIT-Cog substudy. Of these 432 patients, 13 had dementia at baseline and were therefore excluded from this study. We thus present data of 419

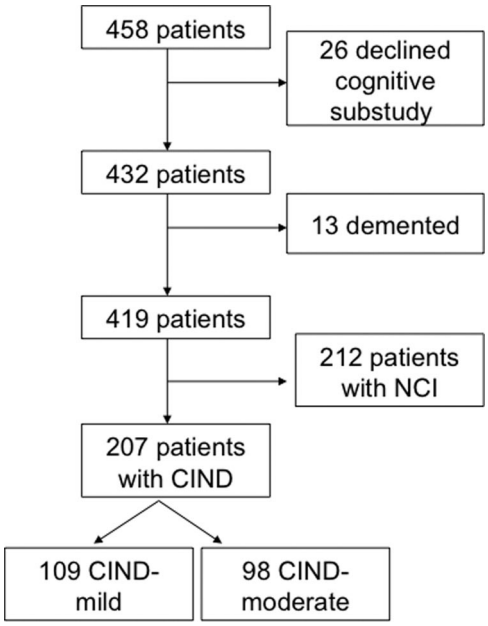

Figure. Study population.

patients (mean age 60±11 years, 32% women) who were followed for a mean of 3.2 years (Figure). There were 212 patients (51%) with NCI, 109 patients (26%) with CIND-mild, and 98 patients (23%) with CIND-moderate. The demographic characteristics of the study population stratified by baseline cognitive status are summarized in Table 1. Older, female, diabetic, hypertensive patients and those with more severe strokes (total/partial anterior circulation infarct) were more likely to have cognitive impairment.

Table 1. Demographic Characteristics of Patient Population Stratified by Baseline Cognitive Status

Characteristic, N (%)	NCI (N=212)	CIND-Mild (N=109)	CIND-Moderate (N=98)	*P*
Age, mean (SD)	54 (10)	64 (10)	66 (11)	<0.0001
Sex, male	163 (77)	67 (61)	57 (58)	0.001
Diabetes mellitus	67 (32)	51 (47)	51 (52)	0.001
Hypertension	141 (67)	87 (80)	79 (81)	0.007
Previous stroke	29 (14)	25 (23)	20 (20)	0.086
Hyperlipidemia	95 (45)	48 (44)	44 (45)	0.989
Ever smoker	81 (38)	42 (39)	19 (30)	0.290
Previous ischemic heart disease	21 (10)	12 (11)	13 (11)	0.679
Previous peripheral artery disease	4 (2)	3 (3)	10 (2)	0.789
Previous angina pectoris	17 (8)	8 (7)	8 (8)	0.970
Previous myocardial infarction	6 (3)	3 (3)	4 (4)	0.875
Stroke subtype				<0.0001
TIA	59 (28)	20 (18)	5 (5)	
POCI/LACI	143 (67)	79 (72)	82 (84)	
TACI/PACI	10 (5)	10 (9)	11 (11)	

NCI indicates no cognitive impairment; CIND, cognitive impairment no dementia; TIA, transient ischemic attack; TACI, total anterior circulation infarct; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; LACI, lacunar infarct.

During the course of the study, 28 patients died, 62 had a vascular event (40 ischemic stroke, 14 myocardial ischemia, 4 intracerebral hemorrhages, 4 peripheral artery disease), and 48 became dependent. The incidence of death was 0.2 per 1000 in NCI patients, 0.9 per 1000 in CIND-mild patients, and 1.4 per 1000 in CIND-moderate patients. The incidence of recurrent vascular events was 1.0 per 1000 in NCI patients, 1.8 per 1000 in CIND-mild patients, and 2.1 per 1000 in CIND-moderate patients. The incidence of dependency was 0.3 per 1000 in NCI patients, 1.9 per 1000 in CIND-mild patients, and 2.2 per 1000 in CIND-moderate patients.

Table 2 summarizes the result of univariate and multivariate Cox proportional hazards analysis predicting dependency, vascular events, and death. In univariate analysis, age, gender, diabetes mellitus, hypertension, stroke subtype, and cognitive impairments were associated with dependency. In multivariate analysis, age, stroke subtype, diabetes mellitus, and all definitions of cognitive impairment were significant predictors of dependency. In univariate analysis, age, diabetes mellitus, CIND, and CIND severity were associated with recurrent vascular events. However, there were no significant predictors of recurrent vascular events in multivariate analysis. In univariate analysis, age, gender, diabetes mellitus, hypertension, and cognitive impairments were associated with death. In multivariate analysis predicting for death, age, diabetes mellitus, and CIND-moderate were all significant predictors of death.

Table 3 summarizes the results of the Cox proportional hazards analysis using domains of cognitive impairment to predict dependency, vascular events, and death. In univariate analysis, all domains predicted for dependency, whereas in multivariate analysis, only visuomotor speed independently predicted dependency (HR=3.49, P=0.002). In univariate analysis, language, visual memory, and visuomotor speed predicted vascular events; however, none remained significant in multivariate analysis. In univariate analysis, language, visual and verbal memory, visuomotor speed, and visuoconstruction were significant predictors of death; however, none remained significant in multivariate analysis.

Discussion

In this study, we determined the prognostic effect of cognitive impairment in poststroke patients without dementia. Specifically, we evaluated the effects of CIND, CIND severity, and domain-specific impairments on dependency, recurrent vascular events, and death.

With regards to dependency, we found that poststroke CIND predicted for dependency. Both CIND-mild and CIND-moderate were predictive of poor functional prognosis when compared with NCI patients. We also found that visuomotor speed independently predicted for dependency after stroke. This is in keeping with a previous study[8] of poststroke patients that showed that visual memory and neglect independently predicted for persistent disturbances in basic activities of daily living, whereas visual perception and construction difficulties independently predicted persistent disturbances in instrumental activities of daily living.

Table 2. Cox Regression Analysis of Baseline Characteristics Predicting Dependency, Recurrent Vascular Events, and Death

	Dependency (4 Missing)						Vascular Events (1 Missing)						Death					
	Univariate			Multivariate†			Univariate			Multivariate†			Univariate			Multivariate†		
Baseline Cognitive Status	HR	0.95	CI	HR	0.95	CI	HR	95%	CI	HR	95%	CI	HR	95%	CI	HR	95%	CI
NCI*	1.00	. . .	. . .	1.00	. . .	. . .	1.00	. . .	. . .	1.00	. . .	. . .	1.00	. . .	. . .	1.00	. . .	. . .
CIND	7.72	3.28	18.2	3.77	1.52	9.37	2.04	1.21	3.42	1.67	0.93	3.00	6.48	2.25	18.7	3.27	1.06	10.1
NCI*	1.00	. . .	. . .	1.00	. . .	. . .	1.00	. . .	. . .	1.00	. . .	. . .	1.00	. . .	. . .	1.00	. . .	. . .
CIND-mild	7.22	2.91	17.9	4.05	1.58	10.4	1.93	1.05	3.54	1.62	0.84	3.12	4.97	1.56	15.8	2.56	0.74	8.83
CIND-moderate	8.32	3.35	20.6	3.41	1.27	9.13	2.15	1.18	3.92	1.74	0.89	3.39	7.98	2.63	24.2	3.81	1.14	12.8
Stroke subtype																		
TIA*	1.00	. . .	. . .	1.00	. . .	. . .	1.00	. . .	. . .				1.00	. . .	. . .	1.00	. . .	. . .
POCI/LACI	4.10	1.27	13.3	2.65	0.80	8.77	2.04	0.97	4.30				2.04	0.61	6.83			
TACI/PACI	5.74	1.44	23.0	4.26	1.02	17.9	1.36	0.41	4.52				2.69	0.54	13.3			
Age	1.07	1.04	1.10	1.05	1.01	1.08	1.03	1.00	1.05	1.01	0.99	1.04	1.06	1.03	1.10	1.03	0.99	1.08
Gender	2.42	1.37	4.27	1.63	0.91	2.92	0.91	0.53	1.55				2.25	1.07	4.72	1.64	0.75	3.60
Diabetes mellitus	2.78	1.55	4.99	2.25	1.23	4.13	1.67	1.02	2.73	1.54	0.94	2.53	3.98	1.75	9.03	2.81	1.20	6.58
Hypertension	2.67	1.13	6.28	1.34	0.55	3.26	1.42	0.77	2.61				4.87	1.16	20.5	2.63	0.60	11.5
Previous stroke	1.69	0.89	3.20				1.61	0.92	2.8				1.29	0.52	3.17			
Hyperlipidemia	0.87	0.48	1.54				0.99	0.60	1.62				1.25	0.60	2.62			
Ever smoker	0.59	0.31	1.13				0.78	0.46	1.34				1.50	0.72	3.16			
Previous ischemic heart disease	1.40	0.63	3.13				0.79	0.34	1.82				2.30	0.93	5.67			
Previous peripheral artery disease	0.79	0.11	5.75				0.58	0.08	4.17				1.46	0.20	10.7			
Previous angina pectoris	1.90	0.85	4.23				1.03	0.44	2.39				2.05	0.71	5.90			
Previous myocardial infarction	0.61	0.08	4.41				0.41	0.06	2.95				4.09	1.23	13.5	3.09	0.45	1.61

HR indicates hazard ratio; CI, confidence interval; NCI, no cognitive impairment; CIND, cognitive impairment no dementia; TIA, transient ischemic attack; TACI, total anterior circulation infarct; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; LACI, lacunar infarct.

*Reference group.

†Adjusted for treatment allocation.

In the present study, we found that CIND predicted poor survival. This is in agreement with both population-based[2,9] studies and poststroke studies[3] in which CIND predicts poor survival, and with studies of PSD that have shown that PSD increases the risk of death by 2- to 6-fold.[26,27] In addition, CIND severity was differentially predictive of poor survival, with CIND-moderate patients 3 to 4 times more likely to die compared with NCI patients, whereas CIND-mild patients had a nonsignificant increase in risk. This novel finding is in line with our previous study that showed that CIND severity is a prognostic factor for incident dementia in poststroke patients.[6] In our study, there were no independent cognitive domains that predicted for death. This is in contrast to a previous study[3] of poststroke outcomes, where deficits in executive functions and visuospatial/construction abilities independently predicted poor survival. We believe that the difference in findings could be caused by both the conservative use of a Bonferroni adjustment and by the relatively lower rates of death in our study (2 deaths per 1000 patient-years versus 59 per 1000 patient-years in the earlier study), which could in turn be a reflection of our differing study lengths (5 years versus 12 years).

In this study, we found no association between CIND, CIND severity, or individual domains of impairment and recurrent vascular events. Although there have been no previous studies that have analyzed the association between poststroke CIND and recurrent vascular events, PSD has previously been shown to increase the risk of recurrent vascular events.[4] There remains some controversy regarding the role of PSD in recurrent vascular events, as leukoaraiosis has been shown to be more predictive than is PSD for recurrent vascular events.[27]

Our study has several limitations. The inclusion/exclusion criteria limit recruitment to those without dominant upper-limb paralysis and who had a baseline mRS $\leq$3. This may limit the generalizability of our findings, as these criteria have resulted in a younger population in ESPRIT than in most stroke populations. Information pertaining to the baseline National Institute of Health Stroke Scale (NIHSS) score was unavailable, and therefore we were unable to control for neurological impairments among this stroke cohort. However, we used the Oxfordshire Community Stroke Project stroke subtype classification as a means of controlling for stroke severity in our analysis. An additional limitation to our

Table 3. Cox Proportional Hazards Models of Domains of Cognitive Impairment Predicting for Dependency, Vascular Events, and Death

	Dependency		Vascular Events		Death	
Univariate	HR	*P*	HR	*P*	HR	*P*
Attention	2.77	0.006	1.11	0.798	2.57	0.055
Language	2.94	0.003	2.16	0.018	3.60	0.005
Verbal Memory	2.47	0.009	1.51	0.159	3.45	0.006
Visual Memory	2.04	0.014	1.79	0.011	2.97	0.004
Visuoconstruction	3.52	<0.001	1.51	0.069	2.58	0.012
Visuomotor Speed	6.78	<0.001	2.12	0.001	3.29	0.003
	Dependency†		Vascular Events‡		Death§	
Multivariate*	HR	*P*	HR	*P*	HR	*P*
Attention	1.04	0.925				
Language	1.67	0.190	2.17	0.027	2.33	0.072
Verbal Memory	1.45	0.325			2.83	0.027
Visual Memory	1.05	0.870	1.32	0.314	1.74	0.155
Visuoconstruction	1.18	0.215			1.26	0.590
Visuomotor Speed	3.49	0.002	1.48	0.176	1.41	0.444

HR indicates hazard ratio.

*Multivariable models included domains of cognition individually in each regression model along with treatment allocation as well as variables that were significant at the univariate stage of analyses.

†Adjusted for stroke subtype, age, sex, diabetes mellitus, hypertension, as well as the treatment allocation.

‡Adjusted for age, diabetes mellitus, and treatment allocation.

§Adjusted for age, sex, diabetes mellitus, hypertension, previous myocardial infarction, as well as treatment allocation.

study was that the majority of patients had baseline computed tomography as opposed to magnetic resonance imaging scans, which are superior in the determination of stroke subtypes. We were also unable to control for prestroke dependency. However, we hypothesize that the inclusion criteria of mRS <3 would limit the effect of prestroke dependency in our study population. Furthermore, although the cognitive battery utilized was validated by administration to an elderly community population in Singapore, more studies need to be performed using other cognitive instruments to confirm the predictive abilities of the CIND-moderate classification. In addition, we recognize that our classifications of CIND did not adopt the typical threshold of less than 1 standard deviation from the mean, but instead adopted the usual MCI threshold of <1.5 standard deviations from the mean. Hence, additional studies are needed to validate the operationalized criteria for CIND in different populations that are at high risk of developing dementia. Furthermore, we did not utilize MCI subtypes (amnestic single-domain MCI, amnestic multiple-domain MCI, nonamnestic single-domain MCI, nonamnestic multiple-domain MCI) in our analysis, as the number of outcomes was small. In addition, we chose to examine CIND and not MCI, as strokes may produce a spectrum of cognitive changes, but may not necessarily produce prominent amnesia, as is emphasized in the MCI subtypes. Therefore, larger studies may be required to examine the comparative predictive abilities of MCI and CIND subtypes. Lastly, the use of the conservative Bonferroni correction method in all analyses pertaining to domain-specific impairments may underestimate the contributions of these domains. In this study, without the use of a correction method, there was an effect of the language domain on vascular events as well as the verbal memory on death. However, we suggest that such findings require additional confirmation. In conclusion, we suggest that CIND severity is predictive of recurrent dependency and death in a highly selected population of nondisabled ischemic stroke patients.

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III

Why is cognitive impairment associated with negative health outcomes?

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Appendix with Tables S1-S6 is available (additional methods, results, and tables)

Author Contributions

KN performed the statistical analysis and wrote the manuscript. CIND and SCI status was derived by BC while dementia outcomes were derived by ALF and KN. LF, MG, and NLP were responsible for the conceptualization and implementation of the study. BC, ALF, AB, LF, MG, and NLP critically appraised the draft.

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Abstract

OBJECTIVE: To test two hypotheses that explain why cognitive impairment no dementia (CIND) predicts negative health outcomes: 1) the underlying genes and shared environment that predispose persons to having CIND also predispose to negative health outcomes and 2) persons with CIND have more difficulties with medication (DWM) which predispose them to have negative health outcomes.

METHODS: Members of the Swedish Twin Registry aged 65 and above underwent the telephone cognitive screening instrument (TELE) or if impaired, an informant interview (Blessed Dementia Rating Scale (BDRS)). Ordinal cognitive scores (ORD), CIND, and Subjective Cognitive Impairment (SCI) statuses were derived from the TELE and BDRS. The outcomes of dementia, death, and hospitalization were ascertained using both the National Patient Register and the Cause of Death Register. In order to test hypothesis 1, logistic regression models with correction for generalized estimating equations (GEE) were compared to conditional logistic models within MZ pairs. In order to test hypothesis 2, Cox regression models with and without DWM were compared.

RESULTS: In 12835 non-demented individuals, ORD scores and CIND status predicted dementia, death, and hospitalization in GEE analyses but not in within-pair analyses. SCI predicted dementia in both GEE and within-pair analyses but predicted hospitalization only in GEE analyses. Difficulties with medication predicted dementia and hospitalization in only Cox analyses with GEE adjustments and predicted mortality in both GEE and within-pair analyses.

CONCLUSION: There are genetic and shared environmental influences in the association between objective cognitive impairment and dementia, death, and hospitalization. However, SCI is associated with dementia independent of genetic and shared environmental confounding. Difficulties with medication use are associated with mortality independent of genetic and shared environmental confounding.

Introduction

The few studies have examined the effect of Cognitive Impairment No Dementia (CIND) or Mild Cognitive Impairment (MCI) on negative health outcomes have shown that it leads to higher rates of institutionalization, dementia , and death[1]. However, studies to date have not investigated the effect of CIND or MCI on the occurrence of vascular events or hospitalization. Little is known about why CIND is associated with negative health outcomes. One possible explanation is that CIND patients have difficulties medication regimens prescribed by their doctors. Another possible explanation is that CIND is purely a marker for an underlying disease process that in itself confers a risk of negative health outcomes. Additionally, there is no clear consensus on the role of Subjective Cognitive Impairment (SCI) in the pathogenesis of dementia. No studies have examined the effect of SCI on outcomes other than cognition.

Twin models provide a framework to study the association between an exposure of interest and an outcome while examining the role of genes and environment. Thus far, no studies have used a twin model in order to determine whether genes and environment can contribute to the observed effect of CIND and SCI on negative health outcomes. Therefore in this study, we aim to use a twin model to determine the association between CIND and SCI and the negative health outcomes of hospitalization, vascular events, dementia, and death. In addition, we explore the role of difficulties with medication in the association between CIND or SCI and negative health outcomes.

Methods

<u>Participants</u>

Participants in this study were part of HARMONY, a study that derived its participants from the Swedish Twin Registry (STR) [2]. Detailed methodology of HARMONY has been described elsewhere [3]. Briefly, all members of the STR aged 65 and above were screened for cognitive impairment in a 2.5 year period beginning March 1998 (screening phase) and a subset were invited to a clinical phase. All participants who were deemed to have dementia or "questionable dementia" were excluded from this study.

Of a total of 13,535 persons that were screened in HARMONY (Figure 1), 700 persons had a diagnosis of dementia or questionable dementia and were therefore excluded from this study. The final study population had 12,835 non-demented persons (mean ±SD age 73±6; 44% male; mean ±SD education 8.7±3.0 years).

Standard Protocol Approvals, Registrations, and Patient Consents

All participants provided informed consent and this study was approved by both the Regional Ethics Board in Stockholm and the Institutional Review Board at the University of Southern California.

Cognitive Screening and Clinical Phase

Cognitive Screening was performed over the telephone with the TELE cognitive screening instrument (details in supplementary section)[4, 5]. For participants who were impaired on the TELE, an informant was interviewed with the Blessed Dementia Rating Scale (BDRS)[6]. The TELE and BDRS were then combined into an ordinal scale (ORD) with scores ranging from 0 (cognitively intact) to 3 (cognitively impaired). Individuals with an ORD score of 3, their twin partner, and a sample of 35 normal control twin pairs were invited to the clinical phase. Clinical diagnoses of dementia were made in consensus conferences in accordance to the DSM-IV criteria[7]. An additional category of "questionable dementia" was added for individuals who did not fulfill one of the three DSM- IV diagnostic criteria, but did exhibit at least two of the criteria: memory problems, problems in another area of cognition, or functional impairments.

Cognitive Status

Cognitive status was classified in three ways: two measures of objective cognitive impairments (OCI), ORD score and CIND, and one measure of SCI. Participants were classified as having CIND if they performed at least two standard deviations below the age and education adjusted means in any of the four cognitive tasks in the TELE. Participants were classified as having SCI if they had reported memory change within the last three years. Being classified as having CIND did not preclude being classified as SCI or having an ORD score of 3 and vice versa. Detailed methodology on the derivation of CIND and SCI status is summarized in the supplementary material. Difficulty with medications (DWM) was derived from a self-reported answer to the question "Have you had problems with taking your medication".

Negative Health Outcomes

In this study, the main study outcomes were derived from population-based registers. Information pertaining to dementia and vascular events were derived from the National Patient Register (NPR)[8] and the Cause of Death Register (CDR) [9]. Information pertaining to hospitalization was derived from the NPR only. Information in the registries as available until the following dates: NPR – Dec 31st 2009, CDR – Dec 31st 2008. Information on death was available until Dec 31st 2010. Vascular event was a composite end point which included seven different diagnoses: hemorrhagic stroke, ischemic stroke, transient ischemic attacks, myocardial infarctions, unstable angina, stable angina, and ischemic heart disease. Further information on the registries and the specific International Classification of Diseases codes included for the outcomes of dementia and vascular events can be found in the appendix.

Interpreting Twin Analyses

Twin studies are an appropriate framework to study genetic and shared environmental influences on a particular disease. Twin studies assume that dizygotic twins (DZ) share 50% of their genes while

monozygotic twins (MZ) share 100% of their genes. All twins share 100% of their shared environment. Analyses in studies using twins control for this relatedness either by using General Estimating Equations (GEE) which adjusts the confidence intervals to account for the correlation within pairs or by performing within-pair analyses which use the healthy co-twin as a naturally matched control to the case, resulting in estimates and confidence intervals adjusted for familial factors. Comparing the GEE analyses to the within-pair analyses allows one to test whether genetic and shared environmental confounders influence the association of interest.

Statistical Analysis

The associations between demographic characteristics and ORD score were determined with analysis of variance or chi-squared analysis as appropriate. Multivariate regression analyses predicting the outcomes of interest were performed in three different ways: 1) Cox Regression Analysis with GEE adjustments (Cohort Cox); 2) Logistic Regression Analysis with GEE adjustments (Cohort Logistic); and 3) Co-twin controlled Conditional Logistic Regression Analysis in which twins discordant for both cognitive status and outcome are analyzed in a matched case-control fashion in MZ Twins (within-pair analysis). In the within-pair analyses, pairs in which the control twin was not alive when his or her partner became demented, was hospitalized, or experienced a vascular event were excluded from the analyses.

All models were adjusted for age, gender, and education. Additionally, models for dementia adjusted for having had a prior stroke while all other models adjusted for a prior vascular event. Additional analyses stratified by time to dementia (within the first 5 years of screening and at least 5 years after screening) were performed. Analyses were performed on Stata version 11.0[10], and significance was determined with a two-tailed alpha of 0.05.

Results

Table 1 summarizes the demographic characteristics of the study population stratified by ORD score. Persons with more cognitive impairment were more likely to be older, less educated, and performed worse on the TELE.

Dementia

There were 993 incident cases of dementia, of which 314 were within 5 years of cognitive screening. In both Cohort Cox and Cohort Logistic regression analyses, there was a dose response relationship between the ORD score and the risk of dementia, with persons with ORD 3 having a 3 to 4 times increased risk of dementia compared to persons with ORD 0 (Table 2). However, in within-pair analysis, there was no longer a significant association between ORD score and risk of dementia. Similarly, persons with CIND had an increased risk of dementia in cohort analyses, but did not exhibit an increased risk of dementia in within-pair analyses. In contrast, persons with SCI demonstrated increased risk of dementia in both cohort and within-pair analyses, suggesting that the association between SCI and dementia is not confounded by genetic and shared environmental factors.

DWM resulted in an increased risk of dementia in cohort Cox regression analyses but not in cohort logistic analyses. Incorporating the information about DWM within the same model as cognitive status results in lower estimates for the cognitive exposures; it also results in DWM no longer predicting dementia (Appendix). This suggests that DWM is one of the mechanisms by which cognitive impairment progresses to dementia. Table 3 summarizes the results of Cox regression analyses predicting dementia within the first 5 years or after 5 years of screening. Measures of OCI have larger effects in the short term (first 5 years) while SCI has a larger effect in the long term (after 5 years).

Mortality

A total of 5,125 study participants died during follow-up. In both Cohort Cox and Cohort Logistic regression analyses, there was a dose response relationship between ORD scores and mortality, with persons with ORD 3 having a two to three times increased risk of death as compared to persons with ORD 0 (Table 4). Similarly, persons with CIND were also at increased risk of mortality in cohort analyses. However, in within-pair analyses, OCI was no longer predictive of death, suggesting that genetic and shared environmental factors may influence the association between OCI and mortality. DWM was a strong predictor of mortality in cohort analyses and also predicted mortality in within-pair analyses. Including DWM in models predicting mortality reduces the estimates associated with the ORD score, but does not remove the independent association between difficulties with medication and mortality (Appendix). There was no association between SCI and mortality.

Hospitalization and Vascular Events

Hospitalization

A total of 10,184 persons were hospitalized for any cause, including dementia, at a mean of 6.6 ± 3.0 years after their cognitive screening. In cohort analyses (table 5), OCI and DWM were predictive of hospitalization in Cohort Cox models, but not in logistic models (Cohort Logistic and within-pair). SCI was predictive of hospitalization in both types of cohort analysis but not in within-pair analysis. Analyses including DWM in the same model as cognitive status did not result in significant changes (Appendix) in the relationship between cognitive status and hospitalization.

Vascular Events

A total of 5,196 persons had experienced a vascular event prior to their cognitive screening, of which 2,307 persons had a previous stroke or TIA. After undergoing cognitive screening, 3,634 people experienced at least one vascular event. There were no significant cognitive predictors of vascular

events in either cohort or within-pair analyses. However, having a prior vascular event was strongly associated with having a later vascular event. Detailed information can be found in the appendix.

Discussion

In this study, we examined two different hypotheses behind why persons with any form of cognitive impairment may have an increased risk of negative health outcomes. The first hypothesis involved persons with cognitive impairment having difficulties with medication use and therefore being at risk of negative health outcomes. We were able to show that DWM was one of the mechanisms by which persons with OCI had an increased risk of dementia and death. In the second hypothesis, we postulated that OCI was a marker of an underlying disease process. Twins who share genetic markers of neuronal frailty should show similar OCIs and similar increased risk of negative health outcomes. Our results that confounding from genetic and shared environmental factors explained some of the association between OCI and dementia, death, and hospitalization support the second hypothesis. Taken together, our results suggest that while difficulties with medication may be one mechanism by which OCI may lead to dementia, other mechanisms, particularly genetic and shared environmental factors, may be more important in the progression of OCI to dementia. While we may not be able to change a person's underlying genetic risk, persons with OCI should be offered tools by which they may be able to reduce medication errors, thereby improving their prognosis. One possible mechanism would be to enable elderly persons to access their medication using multi-dose drug dispensing methods such as Sweden's "Apodos" system[11].

The role of genetics in the progression of MCI to dementia has been summarized recently, with both APOE and SORL1 being the genes that have been extensively studied[12]. A previous twin study from this sample has estimated the heritability of Alzheimer's disease (AD), the most common form of dementia, to be 79% [13]. However, the role of shared environment in the progression of MCI to dementia has not

been as firmly established. The results from the current study further reiterate the need to look for genetic and shared environmental factors that explain the progression of OCI to dementia. They also support the hypothesis that OCI may be a marker of underlying disease processes that can be explained by genetic and environmental factors.

One of the more clinically relevant findings in this study was the increased risk of dementia associated with SCI, which was not explained by genetic and environmental factors. The increased risk of dementia was present in those with SCI regardless of CIND. These results confirm the results from previous studies that show that memory complaints are predictive of cognitive decline and dementia[14-17]. These results also suggest that it may be clinically useful for general physicians to ask the question "Have you noticed ,any change in your memory during the last three years" as a quick screen in order to identify persons at increased risk of dementia. However, this should not be a substitute for more extensive screening.

When looking at the temporal relationship between cognitive status and dementia, we found that OCI is a better indicator of short term (less than 5 years) risk of dementia, while SCI is a better indicator of long term risk of dementia. This temporal gradient between CIND, SCI and dementia, combined with the fact that most longitudinal studies have short follow-ups or small sample sizes, may explain why several studies have been unable to find an association between SCI and dementia [18, 19]. However, our results are in agreement with recent studies on the temporal evolution of AD, which have proposed that the onset of SCI may precede that of OCI [14, 16, 17, 20].

Our finding that OCI was a risk factor for mortality confirms existing reports in the literature [1, 21, 22] . While some of the effects of OCI on mortality was explained by DWM, both OCI and DWM were independent predictors of mortality. This suggests that the increased risk of mortality from having OCI may be both due to difficulties with medication use and due to the fact that OCI may be a marker for an underlying disease process.

In this study, we also found that both objective and subjective cognitive impairment predicted all cause hospitalization. Comparison with other studies is difficult, as no previous reports have examined the association between OCI or SCI and hospitalization. However, one study found that persons with CIND are two and a half more times likely to get institutionalized in nursing homes as compared to persons with no cognitive impairment [1]. In this study, we were able to demonstrate an increased risk in the less severe outcome of all cause hospitalization.

This study has several strengths. It is a large study with a long follow up time and complete ascertainment of outcome. However, this study also has several limitations. The outcome of dementia in this study should be considered to be hospitalization for or death due to dementia, as it was derived from population based registers (NPR and CDR). Previous studies have estimated that only about half of all dementia cases are captured in the registers since hospitalization or death due to dementia as the primary cause is relatively uncommon (the specificity and positive predictive value of dementia diagnoses are close to 100%) [23]. In addition, dementia cases that are captured in the NPR are likely to be more severe. Another limitation is that persons who had an ORD score of 3 in this study fell into the following categories: (a) false positives, meaning that they were visited and worked up and it was determined that they were not demented; (b) those who refused to be worked up; (c) those who were deliberately not worked up because their twin partner was already dead. This introduces the possibility that some of those with an ORD score of 3 were actually demented, and therefore should have been excluded from the study. However, the presence of a dose response relationship between the ORD score and the risk of dementia, death, or hospitalization suggests that the underlying findings are valid. We also performed additional analyses limiting the cohort analyses to the persons in the within-pair analyses to ensure that the underlying findings are valid. In addition, while the use of the TELE facilitates cognitive testing in large scale studies such as HARMONY, they do not allow for subtype analyses that may be undertaken if neuropsychological test batteries were used instead. Unfortunately,

we only have genetic data for those who underwent clinical workup, and therefore are unable to directly examine the role of genes in this study. Lastly, the cross sectional nature of our cognitive data limits our ability to disentangle the effect of cognitive status from that of cognitive decline in attempting to look at the relationship between cognition and negative health outcomes.

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Table 1: Demographic characteristics of study population stratified by ORD score

		ORD 0	ORD 1	ORD 2	ORD 3	P value
		N=7024	N=2959	N=1919	N=933	
Age at screening	Mean(SD)	72(6)	73(6)	76(7)	77(7)	<0.001
Education, 0-7	N(%)	3176(45)	1579(53)	1258(66)	605(65)	<0.001
Gender, Male	N(%)	3099(44)	1336(45)	844(44)	414(44)	0.78
Zygosity*						
Monozygous	N(%)	1684(24)	687(23)	435(23)	232(25)	0.48
Dizygous	N(%)	5246(75)	2226(75)	1439(75)	675(72)	
TELE score	Mean(SD)	17.0(1.2)	15.1(0.9)	12.5(1.5)	11.4(2.5)	<0.001

*Zygosity is unknown for 211 individuals. ORD = Ordinal Score, TELE = Cognitive Screening Instrument

Table 2: Regression analyses predicting dementia.

	N in group (N with DEM)	N=12,835 Cox regression with GEE			N=12,835 Logistic regression with GEE			MZ only, N=3,038 Conditional logistic regression			
		HR	95%	CI	OR	95%	CI	N (DEM)	OR	95%	CI
Cognitive variables											
ORD 0 (Ref)	*7024(336)*	1.00	-	-	1.00	-	-	*1684(78)*	1.00	-	-
ORD 1	*2959(227)*	**1.54**	**1.30**	**1.82**	**1.52**	**1.27**	**1.81**	*687(50)*	1.07	0.53	2.15
ORD 2	*1919(245)*	**2.47**	**2.08**	**2.93**	**2.15**	**1.78**	**2.59**	*435(53)*	0.62	0.22	1.80
ORD 3	*933(185)*	**4.38**	**3.61**	**5.32**	**3.36**	**2.72**	**4.15**	*232(54)*	1.11	0.37	3.39
No CIND, No SCI (Ref)	*4392(181)*	1.00	-	-	1.00	-	-	*1043(36)*	1.00	-	-
No CIND, SCI	*4742(364)*	**1.73**	**1.45**	**2.08**	**1.75**	**1.45**	**2.11**	*1153(97)*	**3.38**	**1.37**	**8.32**
No SCI, CIND	*1194(98)*	**2.20**	**1.72**	**2.82**	**1.96**	**1.51**	**2.54**	*266(25)*	2.83	0.53	15.09

SCI and CIND	*1580(178)*	**2.72**	**2.20**	**3.34**	**2.61**	**2.09**	**3.25**	*356(35)*	1.93	0.54	6.92
No CIND (Ref)	*8993(528)*	1.00	-	-	1.00	-	-	*2162(129)*	1.00	-	-
CIND	*2915(293)*	**1.86**	**1.61**	**2.15**	**1.73**	**1.48**	**2.01**	*657(68)*	1.03	0.45	2.35
No SCI (Ref)	*5080(241)*	1.00	-	-	1.00	-	-	*1193(53)*	1.00	-	-
SCI	*6181(525)*	**1.64**	**1.41**	**1.92**	**1.69**	**1.44**	**1.99**	*1474(132)*	**3.17**	**1.22**	**8.22**
No DWM (ref)	*11908(846)*	1.00	-	-	1.00	-	-	*2812(196)*	1.00	-	-
DWM	*173(23)*	**2.49**	**1.58**	**3.92**	1.01	0.61	1.67	*48(9)*	1.32	0.15	11.67

ORD = Ordinal Score, CIND = Cognitive Impairment No Dementia, SCI = Subjective Cognitive Impairment, VE= Vascular event, MZ= Monozygotic twins, GEE= General Estimating Equations, DWM = Difficulties with medication.

All models adjusted for age, gender, education and previous stroke.

Table 3: Cox regression analysis predicting dementia either within the first 5 years after screening or after 5 years

	Within 5 years of cognitive screen			5 years after cognitive screen		
	N=12,835, N DEM=314			N=10,664, N DEM= 679		
	HR	95%	CI	HR	95%	CI
Cognitive variables						
ORD 0 (Ref)	1.00	-	-	1.00	-	-
ORD 1	**1.49**	**1.03**	**2.15**	**1.56**	**1.29**	**1.89**
ORD 2	**3.60**	**2.60**	**4.99**	**2.15**	**1.74**	**2.65**
ORD 3	**7.99**	**5.71**	**11.17**	**3.05**	**2.36**	**3.96**
No CIND, No SCI (Ref)	1.00	-	-	1.00	-	-
No CIND, SCI	**2.11**	**1.41**	**3.16**	**1.66**	**1.35**	**2.03**
No SCI, CIND	**3.55**	**2.91**	**5.74**	**1.86**	**1.39**	**2.49**

SCI and CIND	**4.22**	**2.75**	**6.49**	**2.35**	**1.84**	**3.00**
No CIND (Ref)	1.00	-	-	1.00	-	-
CIND	**2.73**	**2.08**	**3.56**	**1.61**	**1.35**	**1.91**
No SCI (Ref)	1.00	-	-	1.00	-	-
SCI	**1.52**	**1.13**	**2.06**	**1.69**	**1.41**	**2.02**
No DWM (ref)	1.00	-	-	1.00	-	-
DWM	**2.51**	**1.35**	**4.67**	**2.36**	**1.17**	**4.74**

ORD = Ordinal Score, CIND = Cognitive Impairment No Dementia, SCI = Subjective Cognitive Impairment, BDRS = Blessed Dementia Rating Scale,

TELE= Cognitive Screening Instrument, DEM = Dementia, DWM = Difficulties with medication

All models adjusted for age, gender, education, and previous stroke.

Table 4: Regression analyses predicting death

	N in group (N who died)	N=12,835 Cox regression with GEE			N=12,835 Logistic regression with GEE			MZ only, N=3,038 Conditional logistic regression			
		HR	95%	CI	OR	95%	CI	N (died)	OR	95%	CI
Cognitive variables											
ORD 0 (Ref)	*7024(2264)*	1.00	-	-	1.00	-	-	*1684(566)*	1.00	-	-
ORD 1	*2959(1158)*	**1.13**	**1.05**	**1.21**	**1.12**	**1.01**	**1.23**	*687(251)*	0.80	0.53	1.21
ORD 2	*1919(1132)*	**1.51**	**1.40**	**1.63**	**1.82**	**1.61**	**2.05**	*435(282)*	1.11	0.63	1.97
ORD 3	*933(661)*	**2.03**	**1.84**	**2.25**	**2.96**	**2.48**	**3.53**	*232(172)*	2.03	0.84	4.90
No CIND, No SCI (Ref)	*4392(1477)*	1.00	-	-	1.00	-	-	*1043(375)*	1.00	-	-
No CIND, SCI	*4742(1779)*	**1.08**	**1.00**	**1.16**	0.98	0.89	1.08	*1153(434)*	0.62	0.39	0.96
No SCI, CIND	*1194(494)*	**1.42**	**1.28**	**1.57**	**1.34**	**1.15**	**1.56**	*266(120)*	0.92	0.48	1.74

SCI and CIND	*1580(731)*	**1.35**	**1.23**	**1.48**	**1.40**	**1.22**	**1.60**	*356(160)*	0.87	0.42	1.79
No CIND (Ref)	*8993(3193)*	1.00	-	-	1.00	-	-	*2162(791)*	1.00	-	-
CIND	*2915(1288)*	**1.29**	**1.20**	**1.38**	**1.43**	**1.30**	**1.57**	*657(298)*	0.91	0.57	1.43
No SCI (Ref)	*5080(1786)*	1.00	-	-	1.00	-	-	*1193(446)*	1.00	-	-
SCI	*6181(2447)*	1.00	0.94	1.07	1.00	0.92	1.10	*1474(576)*	0.68	0.44	1.06
No DWM (ref)	*11908(4495)*	1.00	-	-	1.00	-	-	*2812(1077)*	1.00	-	-
DWM	*173(146)*	**2.62**	**2.18**	**3.15**	**5.01**	**3.26**	**7.71**	*48(42)*	Model does not converge		

ORD = Ordinal Score, CIND = Cognitive Impairment No Dementia, SCI = Subjective Cognitive Impairment, VE= Vascular event, MZ= Monozygotic twins, GEE= General Estimating Equations, DWM = Difficulties with medication.

All models adjusted for age, gender, education and previous vascular event.

Table 5: Regression analysis predicting hospitalizations

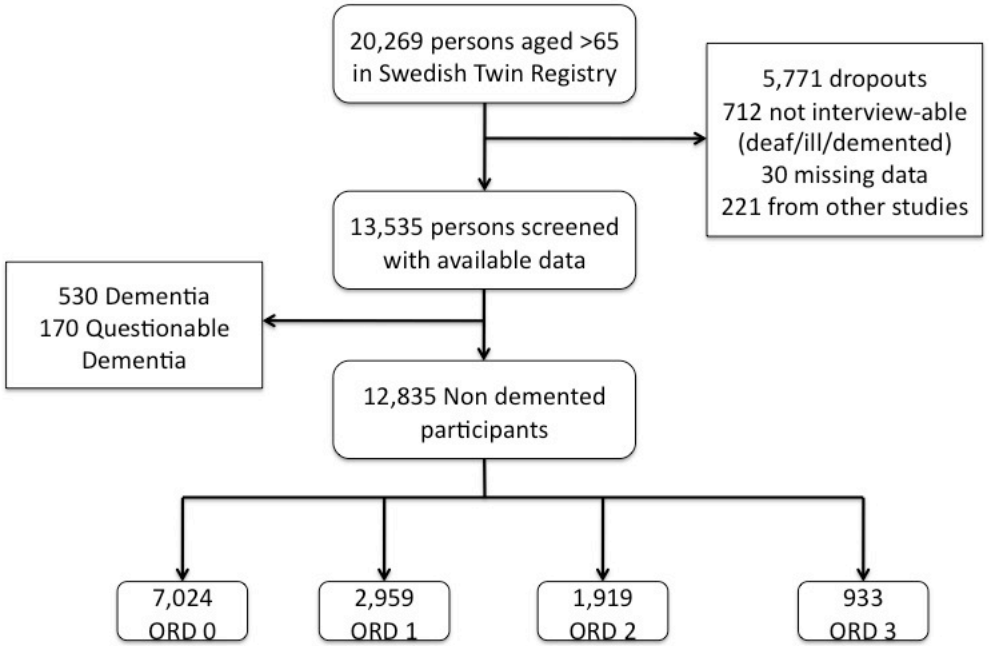
	N in group (N who were hospitalized)	N=12,835 Cox regression with GEE			N=12,835 Logistic regression with GEE			MZ only, N=3,038 Conditional logistic regression			
		HR	95%	CI	OR	95%	CI	N (hosp)	OR	95%	CI
Cognitive variables											
ORD 0 (Ref)	*7024(5417)*	1.00	-	-	1.00	-	-	*1684(1291)*	1.00	-	-
ORD 1	*2959(2368)*	1.05	1.00	1.10	1.07	0.96	1.20	*687(565)*	1.02	0.68	1.53
ORD 2	*1919(1618)*	**1.16**	**1.10**	**1.23**	1.08	0.94	1.26	*435(367)*	0.88	0.44	1.78
ORD 3	*933(781)*	**1.30**	**1.20**	**1.42**	0.92	0.75	1.12	*232(193)*	1.03	0.40	2.63
No CIND, No SCI (Ref)	*4392(3335)*	1.00	-	-	1.00	-	-	*1043(804)*	1.00	-	-
No CIND, SCI	*4742(3828)*	**1.11**	**1.06**	**1.16**	**1.17**	**1.05**	**1.30**	*1153(926)*	0.75	0.48	1.19
No SCI, CIND	*1194(943)*	**1.17**	**1.09**	**1.26**	1.11	0.94	1.31	*266(215)*	0.79	0.40	1.58

SCI and CIND	*1580(1309)*	**1.16**	**1.08**	**1.23**	**1.27**	**1.08**	**1.49**	*356(293)*	1.04	0.52	2.05
No CIND (Ref)	*8993(7050)*	1.00	-	-	1.00	-	-	*2162(1703)*	1.00	-	-
CIND	*2915(2365)*	**1.10**	**1.05**	**1.15**	1.12	0.99	1.24	*657(536)*	0.89	0.56	1.42
No SCI (Ref)	*5080(3887)*	1.00	-	-	1.00	-	-	*1193(929)*	1.00	-	-
SCI	*6181(5024)*	**1.09**	**1.04**	**1.13**	**1.19**	**1.08**	**1.31**	*1474(1191)*	0.75	0.48	1.19
No DWM (ref)	*11908(9405)*	1.00	-	-	1.00	-	-	*2812(2228)*	1.00	-	-
DWM	*173(150)*	**1.46**	**1.21**	**1.77**	0.83	0.51	1.34	*48(42)*	0.18	0.02	1.75

ORD = Ordinal Score, CIND = Cognitive Impairment No Dementia, SCI = Subjective Cognitive Impairment, VE= Vascular event, MZ= Monozygotic twins, GEE= General Estimating Equations, DWM = Difficulties with medication.

All models adjusted for age, gender, education and previous vascular event.

Figure 1: Study Figure



Appendix I

Why is cognitive impairment associated with negative health outcomes?

Table of Contents

Supplementary information on methodology

Cognitive assessment and definition of CIND and SCI

The TELE, a telephone based tool for cognitive screening [1], includes four cognitive tasks which measure different cognitive areas: orientation, attention, episodic memory and reasoning. The orientation task includes 10 items from the Mental Status Questionnaire (MSQ)[2] while attention is measured by counting backwards by threes[3]. Episodic memory is evaluated using three-item recall[4] and reasoning is evaluated with questions about similarities and differences between pairs of nouns[5, 6] In case of a participant's failure to recall all three items, the participant was given the possibility to recall the missed items with a recognition task, which consisted of presenting a list of distractors along with the recall items from which a correct word or words were to be identified. Participants could receive a score that ranges from 0 (worst performance) to 19 (best performance) on the TELE.

Cognitive Impairment No Dementia (CIND) was defined according to current criteria[7] with the following two criteria: 1) *presence of cognitive impairment* defined as a performance two standard deviations below the age and education specific mean at any of the four cognitive tasks of TELE; 2) *absence of dementia* based on clinical diagnosis following the DSM-IV criteria. The age and education specific means of TELE's cognitive tasks were based on the average performance of the dementia-free population classified in eight age and education specific groups.

The TELE also includes a section on cognitive complaints, with both general questions such as "Have you noticed any change in your memory during the last three years?", as well as more specific questions such as forgetting errands, forgetting people's name, forgetting appointments, forgetting known places, and forgetting words.

Subjective Cognitive Impairment (SCI) was defined as any cognitive change in the last three years in the absence of dementia. The specific criteria of SCI were as follows: 1) *presence of subjective*

cognitive complaint as defined as self-reported memory change within the last three years, and 2) *absence of dementia* based on clinical diagnosis following the DSM-IV criteria.

The different classifications of ORD score, CIND, and SCI were not mutually exclusive. The following table describes the overlap between the ORD scores, CIND, and SCI. CIND is derived from age and education adjusted means, while ORD scores do not take age and education into account.

	ORD 0	ORD 1	ORD 2	ORD 3	Total
No CIND, No SCI	3380	830	175	3	4392
SCI, no CIND	3392	1068	243	39	4742
CIND, no SCI	107	479	498	110	1194
CIND and SCI	145	582	641	212	1580

Registry based outcome derivation

The Swedish Twin Registry is linked by the Swedish 10-digit personal identification number to several population-based health registers that may be used as sources of diagnoses for dementia and vascular events. The National Patient Register (NPR) covers all hospital discharges in Sweden since 1987 (with partial coverage since 1964) and the Cause of Death Register (CDR) covers all deaths since 1961. At the time of the study the National Patient Register was available until the end of 2009 and the Cause of Death Register was available until the end of 2008. In the registers, a primary cause of hospitalization or underlying cause of death is recorded as well as up to 6 contributory causes in the NPR and up to 20 contributory causes in the CDR. Diagnoses are recorded with the Swedish versions of International Classification of Diseases (ICD) codes.

Only about half of all dementia cases are captured in the registers since hospitalization or death due to dementia as the primary cause is relatively uncommon. The specificity and positive predictive value of dementia diagnoses are close to 100%[8]. Previous validation studies have shown capture is much better with vascular events such as stroke and myocardial infarctions[9, 10].

ICD codes

Table S1 summarizes the list of ICD codes used in this study. The ICD codes used are from the Swedish version of the ICD. The major difference between the Swedish and the international version of ICD is that in ICD9 the last character of the code is a letter instead of a number. The equivalents are as follows: 0=A, 1=B, 2=C, 3=D, 4=E, 8=W, 9=X.

The outcome of dementia was a composite outcome, incorporating those with Alzheimer's disease, Vascular Dementia or Other Dementia. Similarly, the outcome of vascular event was a composite outcome, incorporating the outcomes of hemorrhagic or ischemic stroke, transient ischemic attack, myocardial infarction, stable or unstable angina, and ischemic heart disease.

Missing Education information

In the 12,835 people included in this study, education was missing for 94 persons (0.7%). To avoid excluding persons with missing data on education from the multivariate analyses, number of years of education was imputed by rounding down from the relevant age group's mean. For example, for a person aged 84 for whom education was unknown, the mean of the age group of 80 to 85 was ascertained (8.64 years), and the nearest 0.5 was then imputed (8.5 years).

Zygosity

In this study, information on zygosity was derived from several sources. DNA information was available for 1,849 twins (14.4%), and registry based records were available for a further 9,864 twins (76.9%). Registry based records were derived from questionnaire and screening reponses to the following question: "During childhood, were you and your twin partner as similar as berries (the Swedish equivalent of 'as alike as two peas in a pod') or not more alike than siblings in general?". For the remaining 1,122 twins, zygosity was determined using answers to the same question during the telephone screen. Twin pairs that did not agree, or where only one member of the pair responded were classified as indeterminate (N=211, 1.6%). Earlier validation studies using DNA have shown that this question is 98% accurate [11].

Supplementary information on results

Distribution of exposures and outcomes in MZ twins

Since only pairs in which there is discordant exposure and discordant outcome information are contributory in within-pair analyses, we have listed the numbers of pairs discordant for outcomes and exposures in the following table.

	Discordant	Concordant (exposed)	Concordant(unexposed)
Exposures	*N pairs*	*N pairs*	*N pairs*
ORD score	390	189	412
CIND	260	56	601
SCI	316	304	220
DWM	17	1	915
Outcomes			
Dementia	89	10	892
Death	288	180	523
Hospitalization	302	606	83
Vascular events	277	97	617

For the within pair analyses, these reduce to the following numbers of pairs in each analysis (table below).

	ORD score	CIND	SCI	DWM
Dementia	89	77	69	76
Death	288	265	240	266
Hospitalization	302	283	258	289
Vascular events	277	258	237	259

Vascular events

The results of regression analyses predicting vascular events is summarized in Table 2. While ORD 2 was a significant predictor of vascular events in Cox Regression analyses, there was no trend within ORD score of increasing severity of impairment conferring additional risk of vascular events. We are therefore unable to conclude if worse performance on ORD scale increases the risk of vascular events. The strongest predictor of vascular events was having a prior vascular event.

Difficulty with medication

Difficulty with medications is one of the possible ways in which persons with CIND may be at increased risk of negative health outcomes. Therefore we examined the effect of difficulties with medications on negative health outcomes in both regression models accounting for cognitive impairment (Tables S3-S6 below), and in independent regression models (Tables 2, 4, and 5 in the main paper and Table S2 in the supplementary section).

Including an indicator of difficulties with medication in the models that predicted dementia (Table S3) reduced the hazards ratios (HR) and odds ratios (OR) for the ORD score and for the combination of SCI and CIND, but not for CIND or SCI scores (Tables 2 versus S3). Difficulties with medication no longer predicted for incidence of dementia. This suggests that while difficulties with medication may be one mechanism by which cognitive impairment may lead to dementia, other mechanisms, particularly genetic and familial factors may be more important in the progression of CIND to dementia.

Including an indicator of difficulties with medication in models predicting mortality (Table S4) reduces the HRs and ORs associated with the ORD score (Table 4 versus S4). However, difficulties with medication remain independently predictive of mortality. This suggests that while some of the effect of CIND on mortality may be explained by difficulties with medication, difficulties with medication itself remains a strong independent predictor of all cause mortality.

In regression models predicting hospitalization (Table S5), including an indicator of difficulties with medication did not significantly change the HRs or ORs of the cognitive exposures (Table 5 versus S5). However, difficulties with medication remained an independent predictor of hospitalization. In regression models predicting vascular events (Table S6), including an indicator of difficulties with medication did not significantly change the HRs or ORs of the cognitive exposures (Tables S2 versus S6). Having had a prior vascular event perfectly predicted for having a vascular event during the study follow up.

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Table S1: ICD codes used in this study

	ICD7	ICD8	ICD9	ICD10
Dementia				
Alzheimer's Disease	305,304	290	290A/B/X, 331A	F00, G30, F03
Vascular Dementia	306	293.0, 293.1	290E	F01
Other Dementia			294B, 290W, 331B/C/X	F02, G311, G318A, F051
Vascular Event				
Hemorrhagic Stroke	331	432-434	432-434	I61
Ischemic Strokes	332	431	431-432	I63
Transient Ischemic Attack	333	435	435	G45X, I66, G46
Myocardial Infarction OR Unstable Angina	420	410-411	410-411	I21, I22
Stable Angina OR Ischemic Heart Disease	420	412-414	412-414	I20, I24, I25

ICD = International Classification of Diseases

Table S2: Regression analysis predicting vascular events

	N in group (N with VE)	N=12,835 Cox regression with GEE			N=12,835 Logistic regression with GEE			MZ only, N=3,038 Conditional logistic regression			
		HR	95%	CI	OR	95%	CI	N (VE)	OR	95%	CI
Cognitive variables											
ORD 0 (Ref)	*7024(1832)*	1.00	-	-	1.00	-	-	*1684(418)*	1.00	-	
ORD 1	*2959(852)*	1.06	0.98	1.15	1.04	0.90	1.21	*687(188)*	0.93	0.59	1.47
ORD 2	*1919(645)*	**1.16**	**1.05**	**1.27**	0.99	0.84	1.18	*435(147)*	0.95	0.56	1.63
ORD 3	*933(305)*	1.14	1.00	1.30	0.70	0.57	0.86	*232(74)*	1.53	0.73	3.22
No CIND, No SCI (Ref)	*4392(1141)*	1.00	-	-	1.00	-	-	*1043(265)*	1.00	-	
No CIND, SCI	*4742(1386)*	0.99	0.92	1.07	0.91	0.79	1.05	*1153(310)*	0.58	0.20	1.69

No SCI, CIND	*1194(317)*	1.06	0.93	1.20	0.85	0.68	1.06	*266(73)*	1.40	0.11	17.26
SCI and CIND	*1580(479)*	0.98	0.88	1.09	0.83	0.69	1.01	*356(104)*	1.29	0.28	5.86
No CIND (Ref)	*8993(2487)*	1.00	-	-	1.00	-	-	*2162(567)*	1.00	-	
CIND	*2915(836)*	1.03	0.95	1.11	0.91	0.79	1.05	*657(185)*	1.37	0.47	4.00
No SCI (Ref)	*5080(1324)*	1.00	-	-	1.00	-	-	*1193(302)*	1.00	-	
SCI	*6181(1825)*	0.97	0.90	1.04	0.94	0.82	1.07	*1474(406)*	0.77	0.26	2.23
No DWM (ref)	*11908(3319)*	1.00	-	-	1.00	-	-	*2812(742)*	1.00	-	-
DWM	*76(173)*	1.15	0.90	1.48	0.93	0.58	1.49	*48(20)*	1.03	0.15	6.85
<u>Demographic variables</u>											

Age (years)	*12835(3634)*	**1.03**	**1.02**	**1.04**	**1.01**	**1.01**	**1.02**	*3038(827)*	1.32	0.33	5.41
Education, 0-7 as ref	*12835(3634)*	0.95	0.89	1.01	0.94	0.83	1.06	*3038(827)*	2.52	0.60	10.63
Gender, male as ref	*12835(3634)*	**0.82**	**0.77**	**0.88**	0.88	0.79	1.00	*3038(827)*	Not applicable		
Prior VE, none as ref	*12835(3634)*	**416**	**271**	**639**	**804**	**521**	**1239**	*3038(827)*	Model did not converge		

ORD = Ordinal Score, CIND = Cognitive Impairment No Dementia, SCI = Subjective Cognitive Impairment, VE= Vascular event, MZ= Monozygotic twins, GEE= General Estimating Equations, DWM = Difficulties with medication.

All models adjusted for age, gender, education and previous vascular event.

Table S3: Regression analyses predicting dementia (with adjustment for DWM)

	N in group (N with DEM)	N=12,835 Cox regression with GEE			N=12,835 Logistic regression with GEE			MZ only, N=3,038 Conditional logistic regression			
		HR	95%	CI	OR	95%	CI	N (DEM)	OR	95%	CI
Cognitive variables											
ORD 0 (Ref)	*7024(336)*	1.00	-	-	1.00	-	-	*1684(78)*	1.00	-	-
ORD 1	*2959(227)*	**1.54**	**1.30**	**1.83**	**1.52**	**1.27**	**1.82**	*687(50)*	0.98	0.46	2.11
ORD 2	*1919(245)*	**2.43**	**2.02**	**2.92**	**2.27**	**1.86**	**2.76**	*435(53)*	0.33	0.09	1.28
ORD 3	*933(185)*	**3.67**	**2.94**	**4.58**	**3.30**	**2.60**	**4.19**	*232(54)*	1.05	0.23	4.89
No CIND, No SCI (Ref)	*4392(181)*	1.00	-	-	1.00	-	-	*1043(36)*	1.00	-	-
No CIND, SCI	*4742(364)*	**1.85**	**1.53**	**2.24**	**1.89**	**1.55**	**2.29**	*1153(97)*	**4.35**	**1.53**	**12.34**

No SCI, CIND	*1194(98)*	**2.34**	**1.83**	**3.02**	**2.16**	**1.66**	**2.82**	*266(25)*	3.20	0.56	18.26
SCI and CIND	*1580(178)*	**2.91**	**2.34**	**3.61**	**2.87**	**2.29**	**3.60**	*356(35)*	2.17	0.55	8.47
No CIND (Ref)	*8993(528)*	1.00	-	-	1.00	-	-	*2162(129)*	1.00	-	-
CIND	*2915(293)*	**1.86**	**1.60**	**2.15**	**1.76**	**1.50**	**2.05**	*657(68)*	0.99	0.39	2.49
No SCI (Ref)	*5080(241)*	1.00	-	-	1.00	-	-	*1193(53)*	1.00	-	-
SCI	*6181(525)*	**1.64**	**1.41**	**1.92**	**1.69**	**1.44**	**1.99**	*1474(132)*	**3.18**	**1.22**	**8.25**
<u>Demographic variables</u>											
Age (years)	*12835(993)*	**1.11**	**1.10**	**1.13**	**1.08**	**1.07**	**1.09**	*3038(235)*	2.82	0.32	24.67
Education, 0-7 as ref	*12835(993)*	1.04	0.91	1.19	1.08	0.94	1.25	*3038(235)*	0.66	0.22	2.01
Gender, male as ref	*12835(993)*	0.96	0.83	1.10	1.15	0.99	1.33	*3038(235)*	Not applicable		

Prior Stroke, none as ref	*12835(993)*	**1.91**	**1.64**	**2.22**	**1.84**	**1.56**	**2.15**	*3038(235)*	**3.18**	**1.25**	**8.10**
No DWM (ref)	*11908(846)*	1.00	-	-	1.00	-	-	*2812(196)*	1.00	-	-
DWM	*173(23)*	1.59	0.99	2.55	0.68	0.41	1.14	*48(9)*	1.31	0.14	12.71

ORD = Ordinal Score, CIND = Cognitive Impairment No Dementia, SCI = Subjective Cognitive Impairment, MZ= Monozygotic twins, GEE= General Estimating Equations, DWM = Difficulties with medication.

All models adjusted for age, gender, education and previous stroke.

Table S4: Regression analyses predicting death (with adjustment for DWM)

	N in group (N who died)	N=12,835 Cox regression with GEE			N=12,835 Logistic regression with GEE			MZ only, N=3,038 Conditional logistic regression			
		HR	95%	CI	OR	95%	CI	N (died)	OR	95%	CI
Cognitive variables											
ORD 0 (Ref)	*7024(2264)*	1.00	-	-	1.00	-	-	*1684(566)*	1.00	-	-
ORD 1	*2959(1158)*	**1.27**	**1.04**	**1.21**	**1.11**	**1.01**	**1.23**	*687(251)*	0.79	0.52	1.21
ORD 2	*1919(1132)*	**1.36**	**1.24**	**1.48**	**1.58**	**1.39**	**1.80**	*435(282)*	1.06	0.56	2.01
ORD 3	*933(661)*	**1.68**	**1.50**	**1.89**	**2.20**	**1.81**	**2.67**	*232(172)*	1.26	0.43	3.69
No CIND, No SCI (Ref)	*4392(1477)*	1.00	-	-	1.00	-	-	*1043(375)*	1.00	-	-
No CIND, SCI	*4742(1779)*	1.03	0.96	1.10	0.99	0.90	1.10	*1153(434)*	0.65	0.41	1.03

No SCI, CIND	*1194(494)*	**1.31**	**1.17**	**1.46**	**1.36**	**1.17**	**1.59**	*266(120)*	0.94	0.49	1.78
SCI and CIND	*1580(731)*	**1.26**	**1.15**	**1.38**	**1.43**	**1.25**	**1.64**	*356(160)*	0.83	0.40	1.74
No CIND (Ref)	*8993(3193)*	1.00	-	-	1.00	-	-	*2162(791)*	1.00	-	-
CIND	*2915(1288)*	**1.26**	**1.18**	**1.35**	**1.42**	**1.28**	**1.56**	*657(298)*	0.99	0.62	1.59
No SCI (Ref)	*5080(1786)*	1.00	-	-	1.00	-	-	*1193(446)*	1.00	-	-
SCI	*6181(2447)*	1.00	0.95	1.07	1.00	0.92	1.09	*1474(576)*	0.69	0.43	1.04
<u>Demographic variables</u>											
Age (years)	*12835(5125)*	**1.10**	**1.09**	**1.10**	**1.16**	**1.15**	**1.17**	*3038(1271)*	**2.77**	**1.09**	**7.08**
Education, 0-7 as ref	*12835(5125)*	**0.92**	**0.87**	**0.98**	**0.91**	**0.83**	**0.99**	*3038(1271)*	1.48	0.88	2.47
Gender, male as ref	*12835(5125)*	**0.67**	**0.63**	**0.71**	**0.58**	**0.53**	**0.64**	*3038(1271)*	Not applicable		

Prior VE, none as ref	*12835(5125)*	**1.80**	**1.69**	**1.91**	**2.50**	**2.29**	**2.72**	*3038(1271)*	**2.20**	**1.41**	**3.42**
No DWM (ref)	*11908(4495)*	1.00	-	-	1.00	-	-	*2812(1077)*	1.00	-	-
DWM	*173(146)*	**2.19**	**1.80**	**2.66**	**3.37**	**2.18**	**5.21**	*48(42)*	Model does not converge		

ORD = Ordinal Score, CIND = Cognitive Impairment No Dementia, SCI = Subjective Cognitive Impairment, VE= Vascular event, MZ= Monozygotic twins, GEE= General Estimating Equations, DWM = Difficulties with medication.

All models adjusted for age, gender, education and previous vascular event.

Table S5: Regression analyses predicting hospitalization (with adjustment for DWM)

	N in group (N who were hospitalized)	N=12,835 Cox regression with GEE			N=12,835 Logistic regression with GEE			MZ only, N=3,038 Conditional logistic regression			
		HR	95%	CI	OR	95%	CI	N (hosp)	OR	95%	CI
Cognitive variables											
ORD 0 (Ref)	*7024(5417)*	1.00	-	-	1.00	-	-	*1684(1291)*	1.00	-	-
ORD 1	*2959(2368)*	1.04	0.99	1.09	1.06	0.95	1.19	*687(565)*	1.07	0.71	1.62
ORD 2	*1919(1618)*	**1.13**	**1.06**	**1.21**	1.12	0.96	1.32	*435(367)*	1.22	0.57	2.64
ORD 3	*933(781)*	**1.25**	**1.14**	**1.37**	1.16	0.91	1.48	*232(193)*	1.42	0.48	4.22
No CIND, No SCI (Ref)	*4392(3335)*	1.00	-	-	1.00	-	-	*1043(804)*	1.00	-	-
No CIND, SCI	*4742(3828)*	**1.12**	**1.07**	**1.17**	**1.19**	**1.07**	**1.32**	*1153(926)*	0.81	0.51	1.29
No SCI, CIND	*1194(943)*	**1.17**	**1.09**	**1.26**	1.15	0.97	1.36	*266(215)*	0.81	0.40	1.61

SCI and CIND	*1580(1309)*	**1.16**	**1.09**	**1.24**	**1.31**	**1.12**	**1.54**	*356(293)*	1.08	0.54	2.15
No CIND (Ref)	*8993(7050)*	1.00	-	-	1.00	-	-	*2162(1703)*	1.00	-	-
CIND	*2915(2365)*	**1.09**	**1.05**	**1.15**	**1.12**	**1.01**	**1.26**	*657(536)*	1.00	0.61	1.63
No SCI (Ref)	*5080(3887)*	1.00	-	-	1.00	-	-	*1193(929)*	1.00	-	-
SCI	*6181(5024)*	**1.09**	**1.04**	**1.14**	**1.17**	**1.06**	**1.29**	*1474(1191)*	0.81	0.51	1.29
<u>Demographic variables</u>											
Age (years)	*12835(10184)*	**1.04**	**1.04**	**1.04**	**1.08**	**1.07**	**1.09**	*3038(2416)*	2.21	0.84	5.84
Education, 0-7 as ref	*12835(10184)*	1.01	0.97	1.05	1.00	0.91	1.10	*3038(2416)*	0.95	0.57	1.59
Gender, male as ref	*12835(10184)*	**0.90**	**0.86**	**0.93**	0.92	0.84	1.02	*3038(2416)*	Not applicable		
Prior VE, none as ref	*12835(10184)*	**2.25**	**2.17**	**2.35**	**5.96**	**5.24**	**6.78**	*3038(2416)*	**5.02**	**2.73**	**9.22**

No DWM (ref)	*11908(9405)*	1.00	-	-	1.00	-	-	*2812(2228)*	1.00	-	-
DWM	*173(150)*	**1.36**	**1.12**	**1.65**	0.60	0.36	1.01	*48(42)*	0.35	0.04	2.86

ORD = Ordinal Score, CIND = Cognitive Impairment No Dementia, SCI = Subjective Cognitive Impairment, VE= Vascular event, MZ= Monozygotic twins, GEE= General Estimating Equations, DWM = Difficulties with medication.

All models adjusted for age, gender, education and previous vascular event.

Table S6: Regression analyses predicting vascular events (with adjustment for DWM)

	N in group (N with VE)	N=12,835 Cox regression with GEE			N=12,835 Logistic regression with GEE			MZ only, N=3,038 Conditional logistic regression			
		HR	95%	CI	OR	95%	CI	N (VE)	OR	95%	CI
<u>Cognitive variables</u>											
ORD 0 (Ref)	*7024(336)*	1.00	-	-	1.00	-	-	*1684(418)*	1.00	-	-
ORD 1	*2959(227)*	1.07	0.99	1.16	1.06	0.91	1.23	*687(188)*	1.58	0.59	4.27
ORD 2	*1919(245)*	**1.15**	**1.04**	**1.27**	1.07	0.89	1.30	*435(147)*	2.48	0.77	7.82
ORD 3	*933(185)*	1.10	0.95	1.27	0.87	0.69	1.11	*232(74)*	1.60	0.26	9.99
No CIND, No SCI (Ref)	*4392(181)*	1.00	-	-	1.00	-	-	*1043(265)*	1.00	-	-
No CIND, SCI	*4742(364)*	0.99	0.92	1.07	0.94	0.81	1.09	*1153(310)*	0.72	0.22	2.32

No SCI, CIND	*1194(98)*	1.06	0.93	1.21	0.90	0.72	1.13	*266(73)*	1.62	0.13	20.18
SCI and CIND	*1580(178)*	0.98	0.88	1.09	0.87	0.72	1.06	*356(104)*	1.48	0.32	6.88
No CIND (Ref)	*8993(528)*	1.00	-	-	1.00	-	-	*2162(567)*	1.00	-	-
CIND	*2915(293)*	1.02	0.94	1.11	0.92	0.79	1.06	*657(185)*	1.55	0.50	4.85
No SCI (Ref)	*5080(241)*	1.00	-	-	1.00	-	-	*1193(302)*	1.00	-	-
SCI	*6181(525)*	0.97	0.90	1.04	0.94	0.82	1.07	*1474(406)*	0.88	0.29	2.68
<u>Demographic variables</u>											
Age (years)	*12835(3634)*	**1.03**	**1.02**	**1.04**	**1.02**	**1.01**	**1.03**	*3038(827)*	1.37	0.33	5.69
Education, 0-7 as ref	*12835(3634)*	0.96	0.89	1.02	0.97	0.83	1.10	*3038(827)*	2.41	0.53	10.97
Gender, male as ref	*12835(3634)*	**0.83**	**0.77**	**0.88**	0.89	0.79	1.01	*3038(827)*	Not applicable		

Prior VE, none as ref	*12835(3634)*	Model did not converge			Model did not converge			*3038(827)*	Model did not converge		
No DWM (ref)	*11908(3319)*	1.00	-	-	1.00	-	-	*2812(742)*	1.00	-	-
DWM, No DWM as ref	*76(173)*	1.12	0.87	1.44	**0.63**	**0.43**	**0.91**	*48(20)*	0.32	0.03	3.22

ORD = Ordinal Score, CIND = Cognitive Impairment No Dementia, SCI = Subjective Cognitive Impairment, VE= Vascular event, MZ= Monozygotic twins, GEE= General Estimating Equations, DWM = Difficulties with medication.

All models adjusted for age, gender, education and previous vascular event.

IV

Selective Serotonin Reuptake Inhibitors (SSRIs) may increase the risk of dementia

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Abstract

BACKGROUND: Few studies have looked at the association between antidepressant medication and risk of dementia, and those that do have not controlled for depressive and cognitive status. While cardiovascular medications have been shown to protect against dementia, little is known about whether persons at high risk are getting these medications

METHODS: Members of the Swedish Twin Registry aged 65 and above were evaluated for Cognitive Impairment No Dementia (CIND), Subjective Cognitive Impairment (SCI), and depression. Information on antidepressant and cardiovascular medication use was determined from the Swedish Prescription Drug Register. Cox proportional hazards models were used to determine whether 1) antidepressant and cardiovascular medication use was associated with dementia, 2) whether these associations changed the relationship between dementia and CIND, SCI or depression, and 3) whether individuals with CIND, SCI, or depression received more antidepressant or cardiovascular medication than their unimpaired counterparts. Subtypes of antidepressant and cardiovascular medications were also evaluated for their association with dementia.

FINDINGS: A total of 11,151 non-demented individuals with information on CIND, SCI and depression status were identified. In this study, we found that antidepressant use, particularly the use of Selective Serotonin Reuptake Inhibitors (SSRIs) were at doubled the risk of dementia regardless of depression. Cardiovascular medications, particularly antihypertensive and lipid lowering agents halved the risk of dementia. Neither antidepressant nor cardiovascular medication use altered the associations between dementia and CIND or SCI. We also found that persons with CIND and SCI received less cardiovascular and more antidepressant medications than their non-impaired counterparts.

INTERPRETATION: As late life onset of depression may be a prodrome of dementia rather than a risk factor, treating patients with depression as a manifestation of prodromal dementia with antidepressants, particularly with SSRIs, may tip them to manifest dementia rather than protect them. In addition, more attention needs to be paid to the need for cardiovascular medication in persons with cognitive impairment in order to prevent dementia.

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Introduction

There has been an ongoing debate as to whether depression is a prodrome or a risk factor for dementia[1]. Recent evidence leans more towards depression being a prodromal symptom of dementia, with a previous study from this study sample suggesting that late-life depression may be a prodrome rather than a risk factor for dementia[2]. Although it has been established that depression is related to dementia development, several studies [3, 4] to date have shown that depression does not have a role in the progression of Mild Cognitive Impairment (MCI) to dementia. However, while trials [5] have estimated the efficacy of antidepressant therapy in ameliorating depressive symptoms in AD patients, few studies have focused on the efficacy of antidepressant therapy in relieving in persons with MCI, Cognitive Impairment No Dementia (CIND), or Subjective Cognitive Impairment (SCI). Additionally, while studies of antidepressant therapy have evaluated efficacy in terms of ameliorating depressive symptoms, only one large study has evaluated the outcome of dementia, and it did not control for depressive or cognitive status [6].

Recently, there has been an evolution in the concepts behind dementia subtypes, with more evidence of mixed pathology rather than 'pure' AD or 'pure' vascular dementia (VAD) in persons with a late life onset of dementia[7]. Several studies have shown that lifestyle factors such as diabetes, hypertension, obesity, and ischemic heart disease increase the risk of dementia. Epidemiologic studies have also shown that the use of cardiovascular medications, particularly antihypertensives and lipid lowering agents, decrease the risk of dementia [8, 9].

In this population based cohort study with 10 years of follow up, we had three main aims. Firstly, we aimed to determine whether use of antidepressant or cardiovascular medications were associated with dementia. Secondly, we aimed to evaluate whether use of antidepressant or cardiovascular medication

changed the association between dementia and either CIND, SCI, or depression. Lastly, we aimed to determine if individuals with CIND, SCI, or depression received more antidepressant or cardiovascular medications compared to their unimpaired counterparts.

Methods

Participants

Participants in this study were part of HARMONY, a study which derived its participants from the Swedish Twin Registry (STR) [10]. The STR is a population based register that comprises over 170,000 Swedish twins born since 1886. Detailed methodology of HARMONY has been described elsewhere [11]. Briefly, all members of the STR aged 65 and above were screened for cognitive impairment in a 2.5 year period beginning March 1998 (screening phase). Participants who were suspected of cognitive impairment, their twin partners, and a subset of cognitively intact controls were invited for a clinical phase in which dementia status was ascertained. All participants who were deemed to have dementia or "questionable dementia" during the clinical phase were excluded from this study. All participants provided informed consent and this study was approved by both the Regional Ethics Board in Stockholm and the Institutional Review Board at the University of Southern California.

Of a total of 20,269 persons aged 65 and above in the STR, 5,771 could not be reached, 712 were reached but could not be interviewed, 30 had missing data, and 221 were recently seen in other studies, resulting in a total of 13,535 persons that were screened in HARMONY (Figure 1). Of these 13,535 persons, 700 persons had a diagnosis of dementia or questionable dementia and were therefore excluded from this study. An additional 1,674 had no CIND or depression information, resulting in a final study population had 11,151 non-demented persons (mean ±SD age 73±6; 45% male; mean ±SD education 8.8±3.3 years).

Cognitive Screening

Cognitive Screening was performed over the telephone with the TELE cognitive screening instrument [12, 13]. The TELE consists of a 10-item mental status questionnaire (MSQ), three other cognitive domains (three word recall, three word pair similarities, counting backwards in threes), and questions about health and daily functioning. The TELE also includes a section investigating cognitive complaints, including a general question investigating subjective cognitive change "Have you noticed any change in your memory during the last three years?". For participants who were impaired on the TELE, an informant was interviewed with the Blessed Dementia Rating Scale (BDRS)[14].

The TELE and BDRS were then combined into an ordinal scale (ORD) with scores ranging from 0 (cognitively intact) to 3 (cognitively impaired). The following are examples of what constituted an ORD score of 3: More than 3 errors on the MSQ; functional impairment in activities of daily living due to memory impairments; failed one third of the items on the TELE or impaired in 2 domains of the MSQ with a BDRS of at least 1.5. These are based on established cutoffs for functional impairment[14].

Clinical Phase

Individuals with an ORD score of 3 were referred for clinical workup. If the participant was suspected of dementia, his or her twin partner was invited for clinical workup regardless of screen status. Additionally, a sample of 35 normal control twin pairs in which both twin members screened negative were included in the clinical phase. The clinical phase comprised of physical and neurological examinations, neuropsychological evaluations including screening for depression, biochemical evaluations, as well as referrals for neuroimaging. Clinical diagnoses of dementia were made in consensus conferences based on the above information in accordance to the DSM-IV criteria[15]. An additional category of "questionable dementia" was added for individuals who did not fulfill one of the

three DSM- IV diagnostic criteria, but did exhibit at least two of the criteria: memory problems, problems in another area of cognition, or functional impairments.

Cognitive and Depressive Status

Participants were classified as having CIND if they performed two standard deviations below the age and education adjusted means in any of the four cognitive tasks in the TELE but did not fulfill the criteria for dementia. Participants were classified as having SCI if they responded positively to the following question "Have you noticed any change in your memory during the last three years?" Participants were classified as having had depression if they fulfilled four or more criteria on the International Diagnostic Interview Short Form (CIDI-SF) adapted to asses lifetime major depression[16, 17], or had score of eight points or above on the eleven item version of the Center for Epidemiologic Studies Depression (CES-D) scale[18].

Medication Exposure

Information about medication use was derived from the Swedish Prescribed Drug Register (PDR), which contains individual-based data for all prescriptions dispensed to the whole population of Sweden (about 9 million inhabitants)[19]. We used information on medication use from the when the registry started on July 1st 2005 to July 1st 2009. In the registry, medications are categorized by the Anatomical Therapeutic Chemical (ATC) Classification system, as recommended by the World Health Organization[20]. Antidepressants were identified by the ATC code N06A, and two different subtypes, tricyclic antidepressants (TCAs) with the ATC code N06AA, and Selective Serotonin Reuptake Inhibitors (SSRIs) with the ATC code N06AB were identified. Cardiovascular mediations were identified by the following ATC codes: C01AA (digitalis), C03A (thiazide diuretics), C03C (loop diuretics), C03D (potassium sparring diuretics), C07A (beta blockers), C08 (calcium channel blockers), C09A (ACE inhibitors), C09C (angiotensin II inhibitors), and C10A (lipid lowering agents). For subtypes of cardiovascular medication,

we combined all the antihypertensives into one subtype (thiazide, loop, and potassium sparring diuretics, calcium channel blockers, ACE inhibitors, and angiotensin II antagonists), and considered digitalis, beta blockers, and lipid lowering agents as separate subtypes. Medication use was stratified into intervals of 6 months corresponding to the 1st and 2nd halves of each calendar year.

Determination of outcomes

In this study, the primary outcome, dementia, was derived from both the National Patient Register (NPR)[21] and the Cause of Death Register (CDR) [22]. The NPR is a national register that records the relevant International Classification of Diseases (ICD) codes for all inpatient (overnight) admissions at all hospitals in Sweden. Information in the NPR was available until the end of 2009, while information in the CDR was available until the end of 2008. However, updated date of death information was available monthly through linkage of STR to the National Population Register, thereby allowing all study participants to be censored until the end of follow up (July 1st 2009). The ICD codes used to define dementia were as follows: codes 304-306 in ICD 7, codes 290, 293.0/.1 in ICD 8, codes 290 A/B/E/X/W, 294B, 331A/B/C/X in ICD 9, and codes F00-F03, F051, G30, G311, and G318A in ICD 10.

Covariates

As prior stroke is a risk factor for dementia, we used the NPR to identify whether study participants had a previous admission for hemorrhagic or ischemic stroke. Demographic information such as age, gender, and education were collected at baseline as part of the study. Education was dichotomized into 0-7 years of education versus more than 7 years of education.

Statistical Analysis

Univariate and multivariable Cox proportional hazards models were used to determine the time to dementia. All multivariable models were adjusted for age at baseline, gender, education, and previous

stroke. Information on medication use was treated as time varying exposure. In both the general and subtype analyses, medication use was considered a dichotomous exposure (yes/no). As the study sample consists of twins, General Estimating Equations (GEE) was used to control for relatedness. Since the PDR began several years after the baseline evaluation, information on medication use is only available on a subset of the total population. Therefore we present the analyses both as a whole cohort, and to a limited subset to of those alive and non-demented at the start of the PDR (July 1st 2005). All participants are considered unexposed before the start of the PDR.

While means and standard errors are presented in Figure 2a-f, the Mann Whitney U test was used to compare the number of prescriptions for antidepressant or cardiovascular medications by CIND, SCI, or depressive status. Analyses were performed on Stata version 11.0[23], and significance was determined with a two-tailed alpha of 0.05.

Results

Of the 11,151 persons in this study, 9,112(81%) participants were alive and non-demented at the start of the PDR. Of the 2,039 who were not included in the subset analyses, 1898 died and 141 were alive but demented. Participants who died during the study period were more likely to be older, male, less educated, have had a prior stroke, CIND, SCI, or depression at baseline (Table 1). Participants who developed dementia after the start of the NPR were more likely to be older, female, less educated, to have had a prior stoke, CIND, SCI, or depression, at baseline (Table 1).

Antidepressants and dementia

In both whole cohort analyses, and analyses restricted to those alive and non-demented at the start of the PDR, antidepressant medication use doubled the risk of dementia (Table 2). In both whole cohort

analyses, and subset analyses, SSRIs more than doubled the risk of dementia while TCAs were not associated with dementia (Table 3).

In both univariate and multivariable models, CIND and SCI were significant predictors of dementia. Antidepressant medication did not modify the association between dementia and CIND (HR 1.87 to HR 1.57) or SCI (HR 1.63 to HR 1.58). However, depression was a significant predictor of dementia in univariate models and multivariable models that did not control for medication use, but was no longer significantly associated with dementia when controlling for antidepressant use (HR 1.24 to HR 1.12).

Cardiovascular medications and dementia

In both whole cohort analyses, and analyses restricted to those alive and non-demented at the start of the PDR, cardiovascular medication use approximately halved the risk of dementia (Table 2). In both whole cohort analyses, and subset analyses, antihypertensive medication use reduced the risk of dementia by approximately 30%, lipid lowering agents reduced the risk of dementia by approximately 50%. Beta blockers and digitalis were not associated with dementia (Table 3). Cardiovascular medication did not modify the association between dementia and either CIND (HR 1.87 to HR 1.57) or SCI (HR 1.63 to HR 1.60). However, depression was a significant predictor of dementia in univariate models and multivariable models that did not control for medication use, but was no longer significantly associated with dementia when controlling for cardiovascular medication use (HR 1.24 to HR 1.16).

Medication use by cognitive or depressive status

Figures 2a, 2b, and 2c summarize the mean and standard errors of antidepressant medications that were dispensed to participants with CIND, SCI, or depression at baseline. Persons with CIND ($p=0.03$), SCI ($p<0.0001$), and depression ($p<0.0001$) received more antidepressants than their non-impaired counterparts. Figures 2d, 2e, and 2f summarize the mean and standard errors of cardiovascular

medications that were dispensed to persons with CIND, SCI, or depression at baseline. Participants with CIND (p=0.0007) and SCI (p=0.03) at baseline received significantly less cardiovascular medications than their non-impaired counterparts. However, there was no difference in the number of prescriptions of cardiovascular medication between those with and without depression at baseline (p=0.84)

Discussion

In this study, we found that antidepressant medication, particularly SSRIs, doubled the risk of dementia. Conversely, we were able to demonstrate that the use of cardiovascular medications, particularly antihypertensives and lipid lowering agents, halved the risk of dementia. We also found that medication use did not alter the association between dementia and CIND or SCI, but that depression was no longer a significant predictor of dementia after adjustment for medication use. Another finding was that persons with CIND and SCI received more prescriptions for antidepressants and less cardiovascular medications than their non-impaired counterparts.

Our finding that SSRIs doubled the risk of dementia agrees with the only large population-based study that has evaluated the effect of antidepressant medication on dementia [6]. Using prescription information from the Danish registry, they showed that compared to persons with only one prescription of antidepressant medication, persons with no prescriptions had 30% of the risk of dementia, and that those with more than one prescription had an increased risk of dementia. However, as their study was entirely registry based, they were not able to correct for cognitive or depressive status in their analyses as we do in the current study.

While antidepressant treatment has been shown to have a strong effect on severely depressed patients, recent meta-analyses indicate that there is a slight or negligible effect on persons with mild to moderate depression[24]. In light of these findings, and in light of the fact that late-onset depression may be a prodrome of dementia rather than a risk factor, one wonders whether the late-onset depression should

be treated at all. While they may alleviate depressive symptoms, antidepressant use may tip an elderly person at high risk to manifest dementia.

A recent editorial[25] has put forth four different neurobiological hypotheses pertaining to the association between depression and dementia. The first hypothesis is that depression directly causes dementia via either excessive glucocorticoid secretion or via the vascular depression hypothesis[26]. If this hypothesis was true, then antidepressant medication should prevent dementia rather than increasing it as seen in this study. The second hypothesis, the "reverse causality" hypothesis, states that depression is an emotional response to an evolving cognitive impairment. However, this hypothesis has also been refuted by a study that is able to demonstrate that depressive symptoms show little change during the development and progression of AD [4].

The third hypothesis is that the same neurodegenerative process that causes the cognitive impairments also causes the depressive symptoms. On a neuronal level, cognitive impairments have been shown to correspond to dysfunction of both cholinergic and serotonergic neurons while depressive symptoms have been linked to the dysfunction of serotonergic neurons [27, 28]. If serotonergic neurons were dysfunctional, treatment with SSRIs may initially improve cognitive status and mood. However, eventually, this will lead to the down regulation of postsynaptic serotonergic receptors and the down regulation of serotonin secretion in the presynaptic cell [29]. These down regulations may result in a deterioration of the cognitive function that may be attributable to serotonergic neuronal activity. Therefore, in addition to the preexisting cholinergic and serotonergic dysfunctions, SSRIs may exacerbate the serotonergic dysfunction, tipping a person to manifest dementia.

The last hypothesis involves a synergistic interaction between depression and cognitive impairment for the development of dementia. However, several studies [3, 4] have already shown that depression does not modify the progression of MCI to dementia. Based on existing literature and the results of this study,

we agree with the third hypothesis that the same neurodegenerative process that contributes to the development of cognitive impairment contributes to the development of depression. Therefore, we propose that elderly persons with depression be treated with antidepressants only if symptoms are severe.

Our results that persons with CIND, SCI and depression receive more antidepressants than their unimpaired counterparts are cause for worry. These results, taken together with the results that antidepressant medications increase the risk of dementia, suggest that the persons at an already high risk of dementia are being exposed to medication that may hasten their conversion to dementia.

Our results that cardiovascular medications, particularly antihypertensives and lipid lowering agents, reduce the risk of dementia confirm the results of previous studies on the same subject [8, 9]. However, the fact that persons with CIND and SCI receive less of these medications than their unimpaired counterparts is further cause for worry. Persons with cognitive impairment may not be as attentive or vocal in their interactions with their physicians, and these results suggest that physicians may need to pay closer attention to the overall medication regimens that their cognitively impaired patients are on.

This study has several strengths. It is a large population-based study with a 10 years of follow up time and complete ascertainment of outcome and medication exposure. In addition, it is the first study that is able to look at the associations between antidepressant use and development of dementia while controlling for cognitive and depressive symptoms.

However, this study also has several limitations. The outcome of dementia in this study should be considered to be hospitalization for or death due to dementia, as it was derived from population based registers (NPR and CDR). Previous studies have estimated that only about half of all dementia cases are captured in the registers since hospitalization or death due to dementia as the primary cause is relatively uncommon (the specificity and positive predictive value of dementia diagnoses are close to

100%) [30]. In addition, dementia cases that are captured in the NPR are likely to be more severe. The cross sectional nature of our cognitive and depression data limits our ability to disentangle the effects of the temporal evolutions of depression and cognitive impairment in this study. The large gap in time between the evaluation of the cognitive and depressive symptoms and the beginning of the PDR may introduce biases in the dataset as persons may have evolved in both depressive and cognitive status. However, we were able to see strong associations between medication use in both whole cohort and the restricted analyses and therefore do not believe that these results are an artifact. Another limitation is that while we are able to ascertain who purchased the antidepressant and cardiovascular medication, we are unable to determine whether these medications are actually consumed. Duration of treatment and the dose of medication could also not be controlled for in both cardiovascular and antidepressant medication.

In conclusion, we were able to show that antidepressant use, particularly SSRIs, increase the risk of dementia even when controlling for depression. Persons with CIND, SCI, and depression receive more antidepressants than their unimpaired counterparts. Additionally, cardiovascular medications halve the risk of dementia, which is important because persons with CIND and SCI receive less cardiovascular medications than their unimpaired counterparts.

Author Contributions

KN performed the statistical analysis and wrote the manuscript. IM derived the depression statuses and wrote the section on derivation of depression status. KJ provided guidance on the medication use and wrote the section on the PDR. IM and AP contributed to the statistical analyses. BC derived CIND and SCI statuses. LF, MG, and NLP were responsible for the conceptualization and implementation of the study. IM, KJ, AP, BC, LF, MG, and NLP critically appraised the draft.

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Table 1: Demographic characteristics of study population stratified by dementia status

		Dementia or death before 1/7/2005	Dementia after 1/7/2005	Non-demented at study end or death before dementia
		N=2039	N=474	N=8638
Age	mean(SD)	77(7)	76(6)	72(5)
Males	N(%)	1095(54)	187(40)	3701(43)
Education (0-7)	N(%)	1139(56)	246(52)	4192(49)
Prior Stroke	N(%)	494(24)	138(29)	1274(15)
CIND	N(%)	623(31)	149(31)	1931(22)
SCI	N(%)	1173(58)	325(69)	4628(54)
Depression	N(%)	461(23)	99(21)	1675(19)

CIND = Cognitive impairment no dementia, SCI = subjective cognitive impairment, SD = Standard Deviation

Table 2: Results of Cox regression analyses predicting for dementia

	Univariate			Multivariable No medication			Multivariable DEP medication			Multivariable CVD medication		
	HR	95%	CI	HR	95%	CI	HR	95%	CI	HR	95%	CI
Whole cohort analysis												
DEP medication -- None	1.00	-	-	-	-	-	1.00	-	-	-	-	-
DEP medication -- Any	**1.89**	**(1.39**	**2.57)**	-	-	-	**2.00**	**(1.45**	**2.73)**	-	-	-
CVD medication -- None	1.00	-	-	-	-	-	-	-	-	1.00	-	-
CVD medication -- Any	**0.53**	**(0.43**	**0.66)**	-	-	-	-	-	-	**0.56**	**(0.45**	**0.70)**
CIND	**1.89**	**(1.62**	**2.19)**	**1.84**	**(1.58**	**2.14)**	**1.54**	**(1.25**	**1.89)**	**1.54**	**(1.25**	**1.89)**
SCI	**1.84**	**(1.58**	**2.15)**	**1.59**	**(1.36**	**1.86)**	**1.55**	**(1.27**	**1.91)**	**1.57**	**(1.25**	**1.89)**
No depression	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Depression before age 65	0.86	(0.62	1.21)	1.22	(0.86	1.73)	0.89	(0.56	1.43)	0.94	(0.59	1.50)
Depression after age 65	**1.30**	**(1.09**	**1.57)**	1.11	(0.91	1.35)	1.04	(0.80	1.35)	1.06	(0.82	1.38)
Those alive at July 1st 2005												
DEP medication -- None	1.00	-	-	-	-	-	1.00	-	-	-	-	-
DEP medication -- Any	**1.89**	**(1.39**	**2.57)**	-	-	-	**1.99**	**(1.45**	**2.73)**	-	-	-
CVD medication -- None	1.00	-	-	-	-	-	-	-	-	1.00	-	-
CVD medication -- Any	**0.53**	**(0.43**	**0.66)**	-	-	-	-	-	-	**0.56**	**(0.45**	**0.70)**
CIND	**1.61**	**(1.32**	**1.95)**	**1.84**	**(1.58**	**2.14)**	**1.54**	**(1.25**	**1.89)**	**1.54**	**(1.25**	**1.89)**
SCI	**1.87**	**(1.55**	**2.28)**	**1.59**	**(1.36**	**1.86)**	**1.55**	**(1.27**	**1.91)**	**1.57**	**(1.28**	**1.93)**
No depression	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Depression before age 65	**0.72**	**(0.45**	**1.14)**	1.22	(0.86	1.73)	0.89	(0.56	1.43)	0.94	(0.59	1.50)
Depression after age 65	1.21	(0.95	1.53)	1.11	(0.91	1.35)	1.04	(0.80	1.35)	1.06	(0.82	1.38)

Multivariable models control for age, education, gender, previous stroke
CIND = Cognitive Impairment No Dementia, SCI = Subjective Cognitive Impairment, CVD = Cardiovascular Medication, DEP = Depression,

HR=Hazards Ratio, CI= Confidence Interval

Table 3: Results of Cox regression subtype analyses predicting dementia

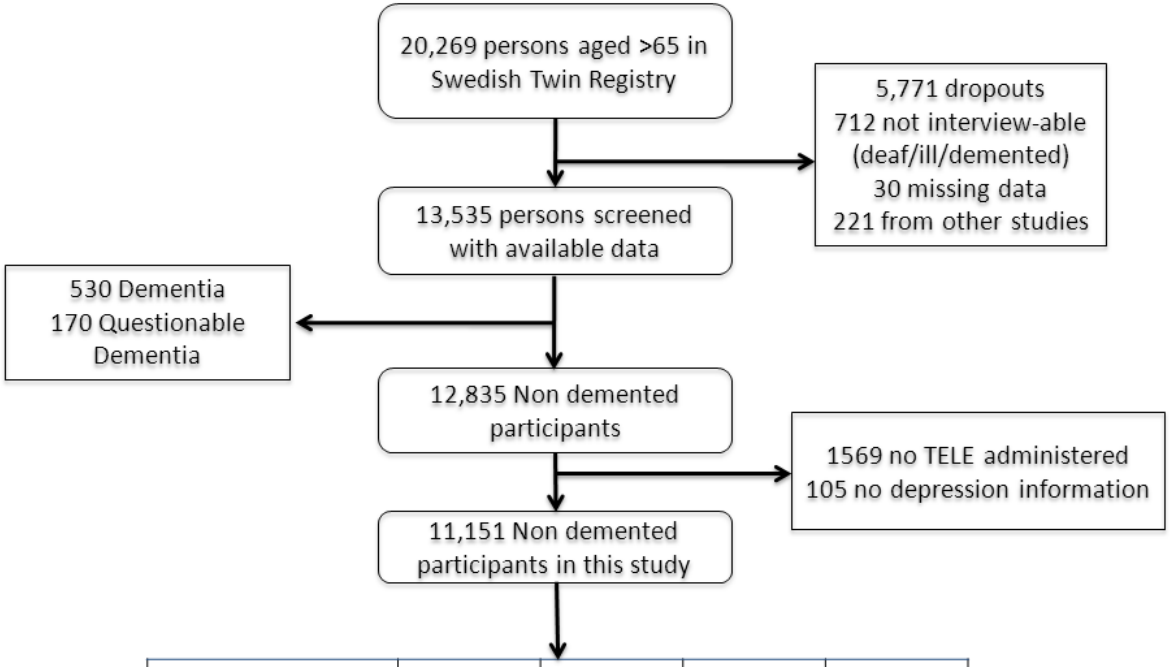
Exposure in the model	Multivariable CIND			Multivariable SCI			Multivariable Depression		
	HR	95%	CI	HR	95%	CI	HR	95%	CI
Whole cohort analysis									
SSRIs	**2.23**	**(1.55**	**3.21)**	**2.17**	**(1.51**	**3.12)**	**2.23**	**(1.55**	**3.17)**
Tricyclic Antidepressants	0.35	(0.05	2.46)	0.35	(0.05	2.48)	0.34	(0.05	2.39)
Antihypertensives	**0.68**	**(0.51**	**0.89)**	**0.68**	**(0.51**	**0.89)**	**0.68**	**(0.51**	**0.89)**
Beta Blockers	0.69	(0.45	1.06)	0.69	(0.45	1.06)	0.69	(0.45	1.06)
Digitalis	1.71	(0.54	5.43)	1.73	(0.54	5.49)	1.71	(0.54	5.45)
Lipid Lowering Agents	**0.48**	**(0.31**	**0.73)**	**0.48**	**(0.31**	**0.73)**	**0.48**	**(0.31**	**0.73)**
Those alive at July 1st 2005									
SSRIs	**2.23**	**(1.55**	**3.21)**	**2.17**	**(1.51**	**3.12)**	**2.23**	**(1.55**	**3.19)**
Tricyclic Antidepressants	0.35	(0.05	2.46)	0.35	(0.05	2.48)	0.34	(0.05	2.39)
Antihypertensives	**0.68**	**(0.51**	**0.89)**	**0.68**	**(0.51**	**0.89)**	**0.68**	**(0.51**	**0.89)**
Beta Blockers	0.69	(0.45	1.06)	0.69	(0.45	1.06)	0.69	(0.45	1.06)
Digitalis	1.71	(0.54	5.43)	1.73	(0.54	5.49)	1.71	(0.54	5.45)
Lipid Lowering Agents	**0.48**	**(0.31**	**0.73)**	**0.48**	**(0.31**	**0.73)**	**0.48**	**(0.31**	**0.73)**

Multivariable models control for age, education, gender, previous strokes

CIND = Cognitive Impairment No Dementia, SCI = Subjective Cognitive Impairment, CVD = Cardiovascular Medication, DEP = Depression,

HR=Hazards Ratio, CI= Confidence Interval

Figure 1: Study Figure



	No SCI No CIND	SCI No CIND	No SCI CIND	SCI CIND
Depression	609	1080	179	367
No Depression	3259	3500	978	1179

Figure 2: Antidepressant and cardiovascular medications prescriptions by CIND, SCI, and depression status.

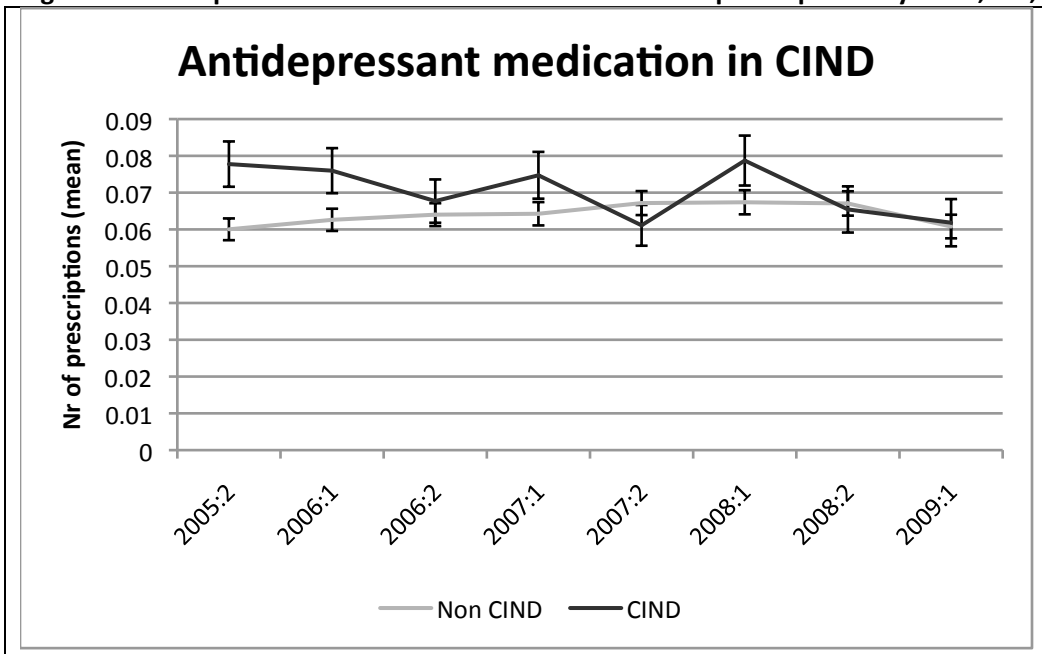


Figure 2a: Antidepressant medication stratified by CIND status.

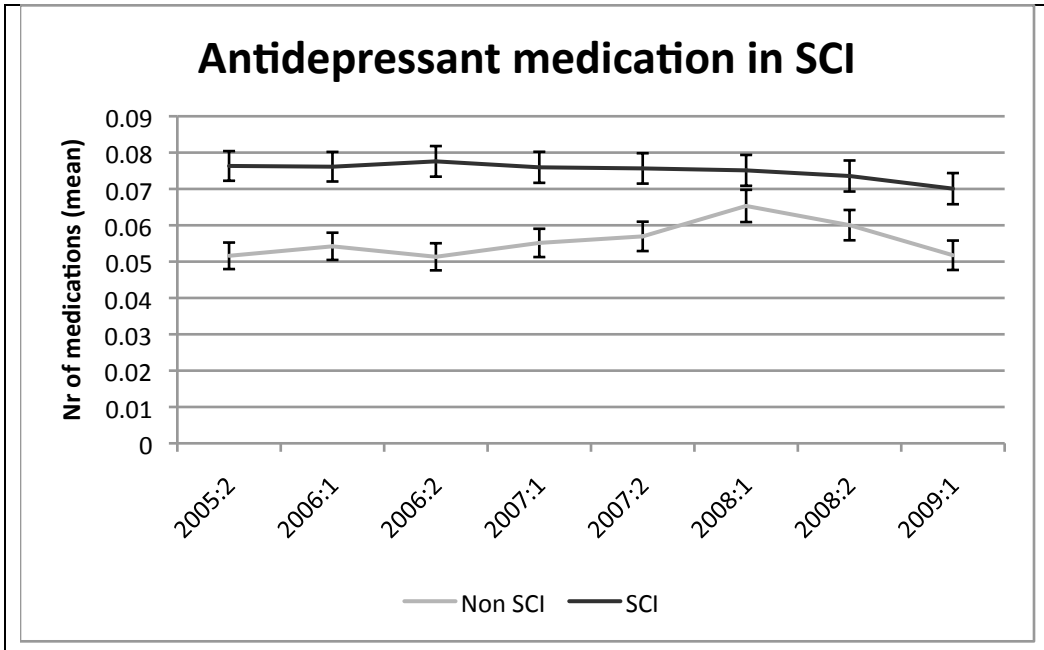


Figure 2b: Antidepressant medication stratified by SCI status.

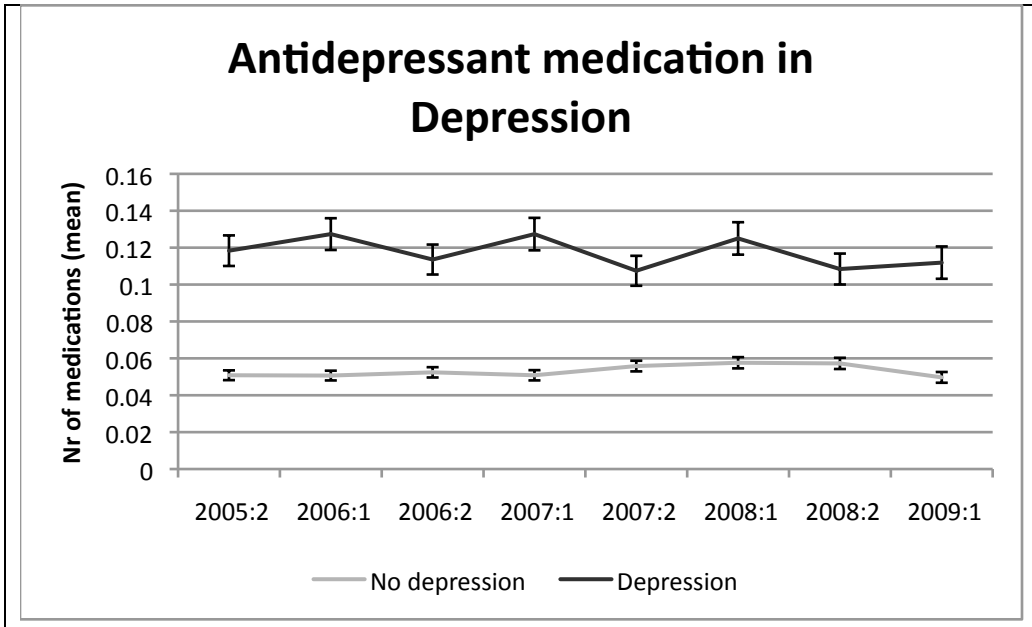


Figure 2c: Antidepressant medication stratified by SCI status.

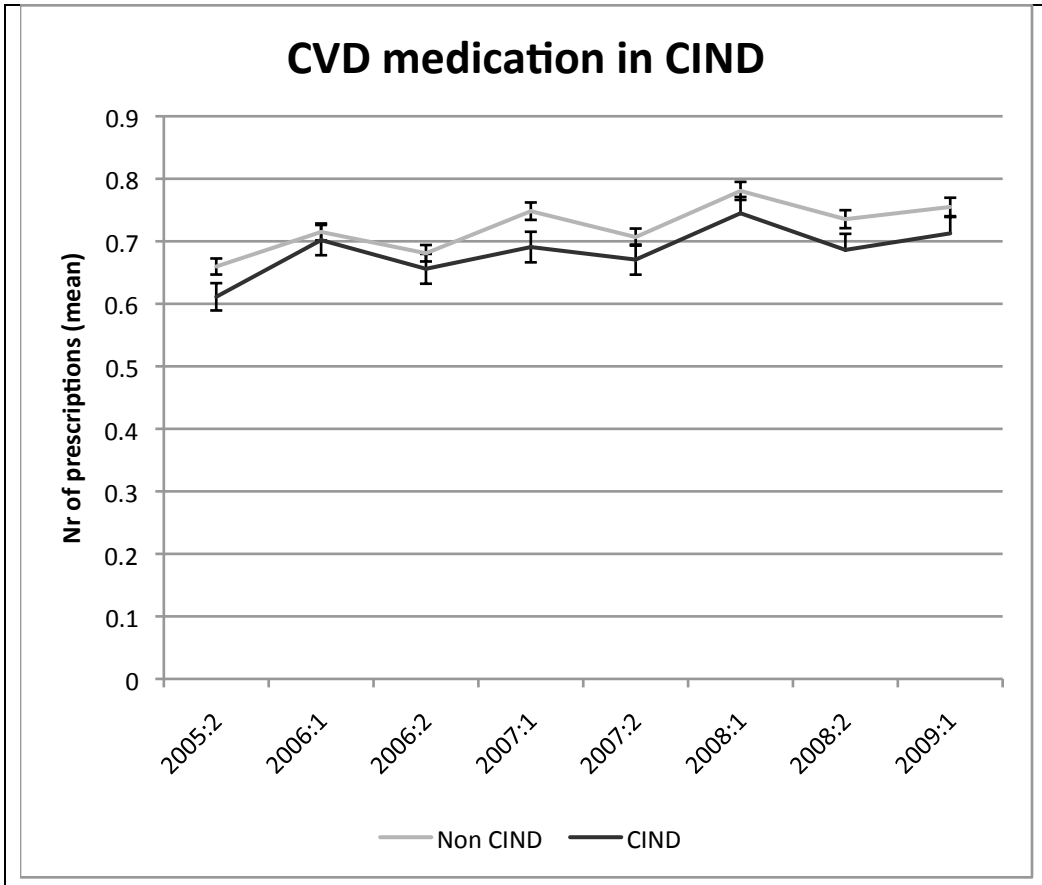


Figure 2d: Cardiovascular medication stratified by CIND status.

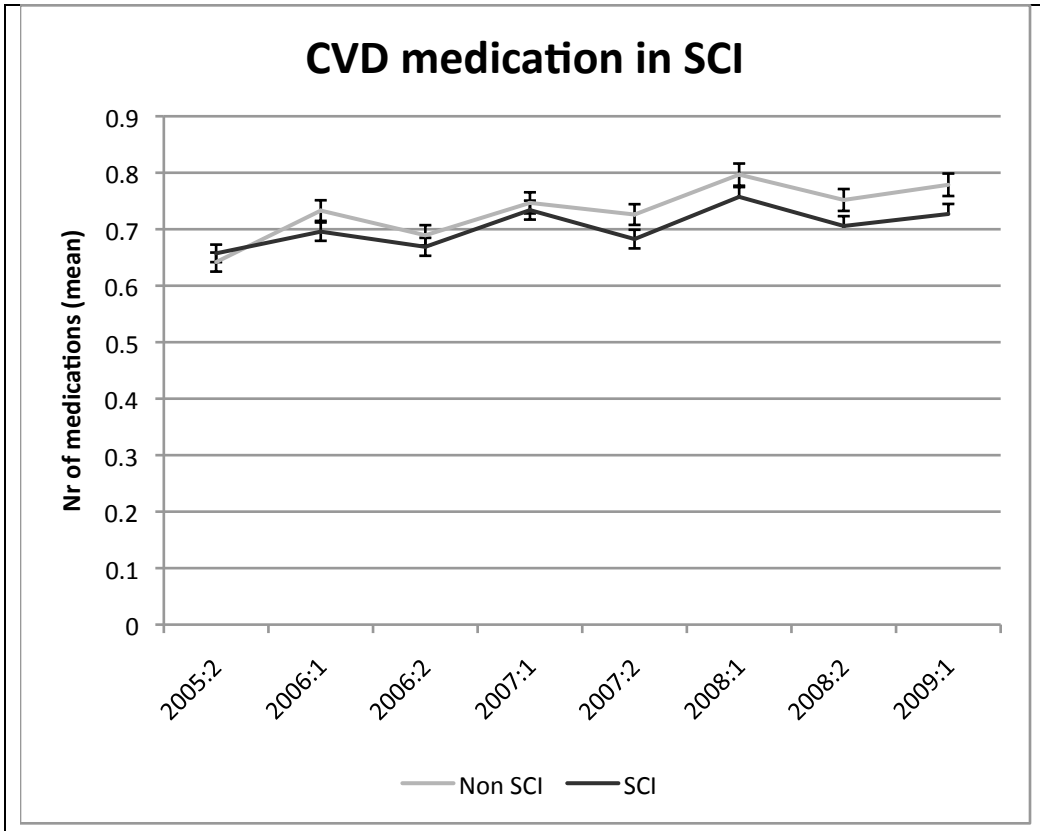


Figure 2e: Cardiovascular medication stratified by SCI status.

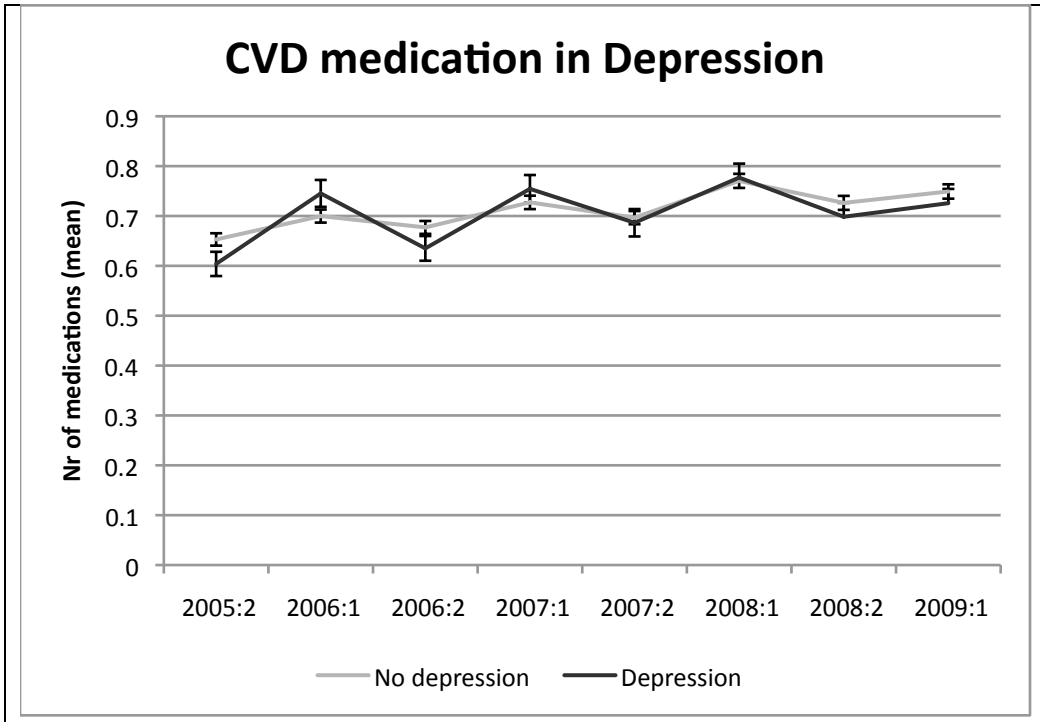


Figure 2f: Cardiovascular medication stratified by depression status.